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Canadian Recommendations for the Prevention and Treatment of Malaria Among International Travellers

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—— 2004 ——

Canadian recommendations for the prevention and treatment of malaria among international travellers

prepared by the

COMMITTEE TO ADVISE ON TROPICAL MEDICINE AND TRAVEL (CATMAT)

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PREFACE

The prevention and treatment of malaria have changed considerably over the last decade, primarily as a result of the development and spread of drug-resistant parasites and a global resurgence of disease.

The following recommendations are guidelines prepared by the Malaria Subcommittee of CATMAT for health care providers to assist travellers in preventing symptomatic malaria and reducing the risk of severe illness or death from this infection.

The ***Travel Medicine Program*** *at Health Canada provides a valuable resource for the traveller and the travel medicine provider. Information concerning malaria and many aspects of the health of travelling Canadians is available at www.travelhealth.gc.ca.*

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PREAMBLE

The Committee to Advise on Tropical Medicine and Travel (CATMAT) provides Health Canada with ongoing and timely medical, scientific, and public health advice relating to tropical infectious disease and health risks associated with international travel.

Health Canada acknowledges that the advice and recommendations set out in this statement are based upon the best current available scientific knowledge and medical practices, and is disseminating this document for information purposes to both travellers and the medical community caring for travellers.

Persons administering or using drugs, vaccines, insect repellents or other products should also be aware of the contents of the product monograph(s) or other similarly approved standards or instructions for use. Recommendations for use and other information set out herein may differ from that set out in the product monograph(s) or other similarly approved standards or instructions for use by the licensed manufacturer(s). Manufacturers have sought approval and provided evidence as to the safety and efficacy of their products only when used in accordance with the product monographs or other similarly approved standards or instructions for use.

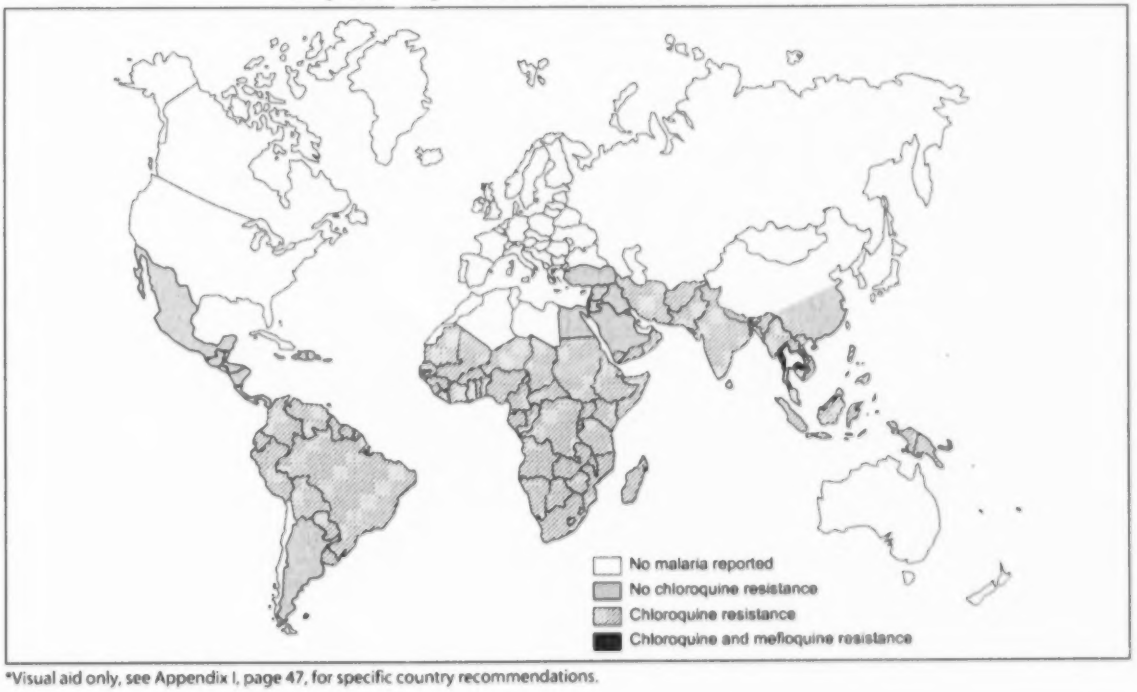
1. INTRODUCTION

Malaria is a common and serious infection caused by four species of the genus *Plasmodium*: *Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale*, and *Plasmodium malariae*. Infection with *P. falciparum* can be fatal, and infections caused by *P. vivax* and *P. ovale* can relapse from latent liver stages. All species of malaria are transmitted by the bite of an infected female *Anopheles* mosquito. Rarely, transmission may occur by blood transfusion, by shared needle use, or congenitally from mother to fetus. The disease is characterized by **FEVER** and "flu-like" symptoms such as myalgias, headache, abdominal pain, and malaise. Rigors and chills often occur. The classically described alternate-day fevers or other periodic fevers are often not present. Severe malaria due to *P. falciparum* may cause seizures, coma, and renal and respiratory failure, and may lead to death. Malaria deaths are frequently the result of delays in the diagnosis and treatment of the infection.

THE SYMPTOMS OF MALARIA ARE NON-SPECIFIC, AND DIAGNOSIS IS NOT POSSIBLE WITHOUT A BLOOD FILM.

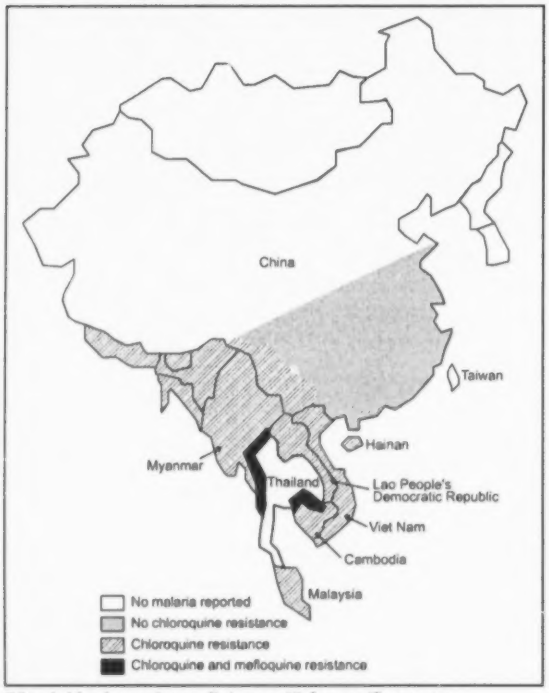
The widespread resistance of *P. falciparum* to chloroquine has complicated the prevention and treatment of malaria. Drug-resistant strains of malaria are now common in much of the world. The maps in Figures 1a and 1b indicate the geographic distribution of *P. falciparum* malaria based on patterns of resistance. These regions require frequent updating as the malaria situation continues to evolve.

Figure 1a
Map showing malaria-endemic zones worldwide*



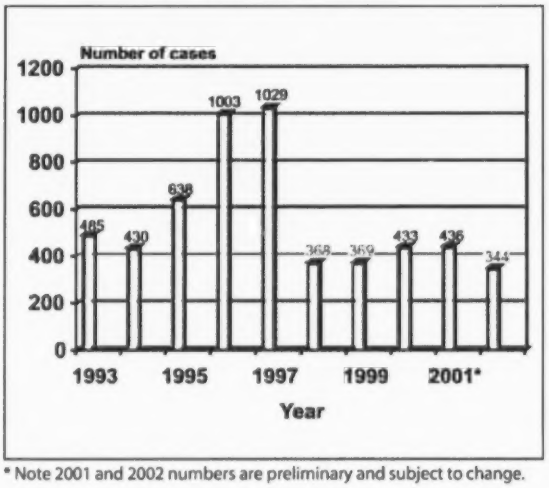
*Visual aid only, see Appendix I, page 47, for specific country recommendations.

Figure 1b
Enlarged map of China and Thailand showing patterns of malaria resistance*



*Visual aid only, see Appendix I, page 47, for specific country recommendations.

Figure 2
Trends in reported malaria cases, Canada, 1993-2002



* Note 2001 and 2002 numbers are preliminary and subject to change.

As noted in Figure 2, the number of reported cases of malaria in Canada peaked in 1997 and then decreased. It is anticipated that the cyclical increase in malaria cases will recur. However, it is estimated that only 30% to 50% of cases are reported to public health agencies, and therefore the true number of imported cases into Canada is likely to be substantially higher. This assumption is supported by a recent study of laboratory reporting in two Canadian provinces, where only 52% to 71% of confirmed laboratory cases were reported to Health Canada. Canada's rate of imported malaria continues to be 3 to 10 times the per capita rate of the United States, which may reflect true differences in risk or may be a reporting artefact.

The majority of imported *P. falciparum* cases continue to be acquired in subSaharan Africa, and the majority of *P. vivax* cases are acquired in the Indian subcontinent. The increased number of Canadian malaria cases has been associated with severe and fatal cases. There have been 11 malaria deaths reported since 1997, all due to *P. falciparum*. As well, since June 2001 there have been 25 cases of malaria requiring parenteral quinine for treatment of severe or complicated disease. Factors contributing to all of these severe and fatal cases were noncompliance with or failure to use appropriate chemoprophylactic agents, delay in diagnosis and treatment, and incorrect therapy once a diagnosis had been reached.

Almost all malaria deaths in travellers are due to *P. falciparum*. The overall case-fatality rate of imported *P. falciparum* malaria varies from approximately 1% to 5% and increases to 30% for those > 70 years of age. Progression from asymptomatic infection to severe and complicated malaria can be extremely rapid, with death occurring within 36 to 48 hours. The fatality rate of severe malaria is > 20% even when the disease is managed in modern intensive care units. The most important factors that determine patient survival are early diagnosis and appropriate therapy. The majority of infections and deaths due to malaria are preventable.

2. PREVENTION

Four components of malaria prevention should be discussed with the traveller:

a. the risk of acquiring malaria
b. personal protective measures to prevent mosquito bites
c. chemoprophylactic drugs (where appropriate)
d. the need to seek early diagnosis and treatment of a febrile illness

a. Risk of Acquiring Malaria

All travellers to malarial areas need to be aware of the risk of malaria infection, how they can best protect themselves, and the need to urgently seek medical advice if they have a fever. Travellers staying overnight in rural areas may be at highest risk.

Malaria transmission occurs in most of subSaharan Africa and New Guinea; in large areas of Southern Asia; in parts of Southeast Asia, Oceania, Haiti, and Central and South America; and in limited areas of Mexico, the Dominican Republic, North Africa and the Middle East. Appendix I provides country-specific information on malaria risk and recommended chemoprophylaxis. This information is derived from the World Health Organization (WHO), the Centers for Disease Control and Prevention (CDC), and the International Association for Medical Assistance to Travellers (IAMAT). While this is the most accurate information at the time of publication, many factors, such as variations in local reporting rates and surveillance, may significantly affect the reliability of these data.

Malaria transmission occurs primarily between dusk and dawn, corresponding to the biting habits of the *Anopheles* mosquito. The risk of transmission is increased in rural areas and varies seasonally in many locations, being highest at the end of the rainy season. Risk is proportional to the duration of an individual's exposure. Transmission decreases at altitudes above 2000 m (6500 feet).

Travel to urban and tourist areas of Southeast Asia, and Central and South America are considered to entail minimal risk, whereas urban travel in other malaria-endemic regions, such as subSaharan Africa, the Indian subcontinent, and New Guinea (Papua New Guinea [PNG] and Papua [Irian Jaya]) may be associated with significant risk of infection. In the last decade, the spread of drug-resistant malaria and the prevalence of infection, especially with *P. falciparum*, have grown steadily. For example, malaria cases are at record levels on the Indian subcontinent, where an increasing proportion are due to drug-resistant *P. falciparum*.

Retrospective studies of large numbers of travellers have provided an approximation of malaria risk during a 1-month stay without chemoprophylaxis: Oceania (PNG, Papua [Irian Jaya], Solomon Islands and Vanuatu) 1:30 or higher, subSaharan Africa 1:50, Indian subcontinent 1:250, Southeast Asia 1:1,000, South America 1:2,500 and Central America 1:10,000. It is noteworthy that the highest risk areas for malaria are Oceania, Africa and, to a lesser extent, the Indian subcontinent.

b. Personal Protective Measures to Prevent Mosquito Bites

READERS SHOULD NOTE THAT THE FOLLOWING RECOMMENDATIONS ARE INTENDED FOR CANADIANS TRAVELLING INTERNATIONALLY TO AREAS OF MALARIA RISK AND MAY DIFFER FROM HEALTH CANADA'S (PEST MANAGEMENT REGULATORY AGENCY) RECOMMENDATIONS FOR DOMESTIC USE OF INSECTICIDES AND REPELLENTS.

All travellers to malaria-endemic regions are advised to use personal protective measures to reduce the risk of bites from *Anopheles* mosquitoes. Any measure that reduces exposure to the evening and night-time feeding *Anopheles* mosquito will reduce the risk of malaria. Risk reduction behaviour is maximized by

using an integrated approach involving personal protective measures:

- avoid mosquitoes, e.g., by staying in an insect-proof area during the period of the day when mosquitoes bite.
- prevent the bites of mosquitoes through
  - physical barriers, e.g., clothing, bed nets
  - chemical barriers, e.g., repellents, insecticides

Avoiding Mosquitoes

Important measures to avoid mosquitoes are as follows:

- minimizing entry of mosquitoes into work and accommodation areas. This includes having screens that are in good repair on windows and doors; doors that close properly and tightly; and walls and roof that are "without holes" (C III – evidence-based medicine recommendation, see Appendix II).
- staying in a mosquito-protected area during the time(s) of the day when local mosquitoes are actively biting (C III – evidence-based medicine recommendation).
- not travelling to a locale during the season most strongly (or only) associated with transmission of malaria (C III – evidence-based medicine recommendation).

Physical Barriers

If mosquitoes cannot bite, then malaria cannot be transmitted; the aim is to reduce the amount of unprotected skin available to the mosquito. Approaches to the prevention of bites comprise physical and chemical barriers. Physical barriers include

- **Clothing**: Wearing long-sleeved shirts (sleeves down, buttoned/zipped up, tucked into pants) and long pants (tucked into socks or footwear) may inhibit or prevent mosquito bites. Light-coloured clothing may be less attractive to some mosquitoes and make mosquitoes more noticeable (B II – evidence-based medicine recommendation).
- **Mosquito net**: Sleeping under a mosquito net is well established as a useful barrier against mosquito bites, but mosquitoes may still bite through the mesh (if the traveller's skin is against the net). The treatment (impregnation) of mosquito netting with insecticide (e.g., permethrin) substantially increases the protection afforded by the net (A I – evidence-based medicine recommendation).

Chemical Barriers

Two types of chemical barrier may be used to reduce the risk of malaria: repellents and insecticides. Repellents do not kill mosquitoes but, rather, affect them in such a way that the mosquito will not bite, whereas insecticides act primarily by killing a mosquito upon contact. These approaches are not mutually exclusive, i.e., some products may act as both a repellent and an insecticide:

- **Repellents**: There are a number of repellent chemicals and formulations for skin application available in Canada and an even larger number available in other countries. Repellents available for sale in most (if not all) Western nations have been reviewed for effectiveness and safety on the basis of national regulations by Health Canada's Pest Management Regulatory Agency (PMRA) and, in the United States, by the Environmental Protection Agency. Where testing has been done, some repellents have been found to be more effective than others against certain arthropod species.
  - **DEET**: The repellent DEET (N,N-diethyl-3-methylbenzamide, also known as N,N-diethyl-*m*-toluamide) is generally acknowledged as the most effective of the currently available repellents (A I – evidence-based medicine recommendation). DEET has been used as a repellent since 1946 by the US military and is estimated to be used several hundred million times by North Americans each year alone. Scientific reviews have concluded that, when used as directed, DEET has an excellent safety record (A I – evidence-based medicine recommendation).

    The higher the concentration of DEET in the repellent formulation, the longer the duration of protection; however, this relation reaches a plateau at about 30% to 35%. For a given DEET

concentration, DEET formulations that are "extended duration" (ED), or microencapsulated, provide longer protection times, likely with less DEET absorption. ED DEET is also more cosmetically acceptable. However, these formulations are not currently available in Canada, although they are in the United States.

Regulatory agencies in Western nations may differ regarding the recommended maximum concentration of DEET, especially for children*. However, it must be recognized that, in comparison to Canada, the risks posed by malaria in other parts of the world are substantial. The traveller to a malarious area should employ any and all measures to reduce the risk. CATMAT is satisfied that, for travel outside of Canada where the risk of malaria outweighs the risk of any important adverse reaction to DEET, the threshold for use of DEET should be low.

CATMAT recommends that concentrations of DEET up to 35% can be used by any age group. For children, alternative personal protective measures, such as insecticide-impregnated mosquito nets, should be the first line of defence, especially for infants < 6 months of age. Portable mosquito nets, including self-standing nets, placed over a car seat, a crib, playpen, or stroller provide an insect-protected environment for infants. However, as a complement to the other methods of protection, the judicious use of DEET should be considered for children of any age. Recent medical literature from Canada suggests that DEET does not pose a significant or substantial extra risk to infants and children.

The reapplication intervals on the label of DEET formulations are a general guide only, since there are many variables, such as sweating, affecting the duration of effectiveness. As a general rule, the reapplication interval is a function of mosquito biting activity, so that if biting is noted before the interval on the label has expired, then reapplication of DEET is recommended.

ED DEET formulations (up to 35%) have useful advantages over other formulations and, overall, are preferred (A II – evidence-based medicine recommendation).

DEET/sunscreen combination products are not generally recommended, as DEET can decrease the efficacy of sunscreens by 34%. As well, the recommendations for application of DEET and sunscreens are diametrically opposed (i.e. use sunscreen liberally and often – use DEET sparingly and only as often as required). If application of both is necessary, the Canadian Dermatology Association recommends that the sunscreen be applied first and allowed to penetrate the skin for 20 minutes, followed by application of DEET (A II – evidence-based medicine recommendation).

- **"Natural-based" repellents:** Most repellents containing "natural" products are effective for shorter durations than DEET (Table 1) and for this reason are not considered the preferred products for protecting against mosquito bites. For example, oil of citronella products can repel mosquitoes, but the duration of protection is very short (generally less than an hour, often less than 30 minutes). Therefore, citronella-containing repellents are not recommended (E II – evidence-based medicine recommendation).

  P-menthane-3,8-diol, a synthetic analogue of lemon eucalyptus oil, has been registered as an insect repellent ("OFF! Botanicals Lotion Insect Repellent 1") by the PMRA. However, the period of protection afforded by this product is less than for ED DEET products, and it is not approved for use on children < 3 years of age. There are data to indicate that it is reasonably effective against mosquitoes that carry malaria. *P-menthane-3,8-diol* may be considered a second-line alternative repellent when DEET use is not possible (e.g., for people

* Health Canada's PMRA allows concentrations only up to 30% to be sold; it recommends that concentrations over 10% not be applied to children < 12 years of age and that application only be three times /day.

Table 1.
Comparative efficacy of selected insect repellents

Active ingredient	Formulation	Brand*	Duration of efficacy† (hrs)	Level of evidence
DEET < 10%	Pump spray, aerosol, gel, lotion	Cutter Skedaddle Skintastic (OFF)	1-3	A I
DEET 10%-30%	Pump spray, aerosol, lotion, stick	Cutter Backwoods Cutter Backyard Cutter Outdoorsman Deep Woods OFF! Muskol OFF!	4-6	A I
DEET 20%-35%	Lotion (microencapsulated slow release)	Sawyer Ultrathon	8-12	A I
Citronella oil 5%-15%	Pump spray, lotion, oil, towelette	Buzz Away Green Ban Herbal Armor Natrapel	0.3-0.5 (20-30 min)	E II
Lemon eucalyptus oil 10%-30%	Lotion	OFF! Botanicals Lotion Insect Repellent 1	2-5	A II
Soybean oil 2%	Oil	Bite Blocker	1-4	A II
Bayrepel 10%-20% (Picaridin/ Hepidanin)	Pump spray, aerosol	Autan	3-5 (10%) 8-10 (20%)	A II

*NOTE : These products are presented as examples only and are not necessarily endorsed by Health Canada.

†Most testing of repellency duration under field conditions is performed with *Aedes* species mosquitoes. Data regarding testing of DEET against *Anopheles* mosquitoes demonstrate shorter duration of efficacy, closer to the lower limits of the ranges in this table, compared with *Aedes* mosquitoes. Testing data for citronella oil and soybean oil are available only for *Aedes* species mosquitoes, and testing data for lemon eucalyptus oil and Bayrepel suggest equivalency of repellency between *Aedes* and *Anopheles* species mosquitoes.

allergic to DEET) (A II – evidence-based medicine recommendation).

Soybean oil 2% "Blocker" products are equivalent to 5% to 10% DEET in efficacy, with products repelling mosquitoes for 1 to 4 hours and black flies for 5 to 10 hours. Soybean oil has low toxicity, has no age-associated restrictions on use, and is non-irritating. It may therefore also be considered an alternative to DEET, albeit one with a substantially shorter protection time and without a long history of use. Importantly, CATMAT is unaware of scientific studies in which soybean repellents have been tested for effectiveness against malaria-transmitting mosquito vectors; therefore, soybean repellents are considered, at best, a third-line repellent where malaria presents a significant risk (A II – evidence-based medicine recommendation). Although there are currently four Blocker products containing soybean oil registered and approved for use in Canada (www.biteblocker.ca), they are not widely available in retail outlets.

- **Other, synthetic repellents**: Bayrepel, a piperidine derivative also known as KBR 3023 and marketed under the trade name Autan, has been in use in Europe for several years. It has demonstrated action against a variety of mosquito species, including those that carry the malaria parasite, with durations of protection comparable to 15% to 50% DEET (A II – evidence-based medicine recommendation). Toxicologic analysis suggests no bio-accumulation and rapid renal excretion with no significant toxic effects reported. Although recommended by the WHO and registered with the Environmental Protection Agency (United States) in 2002, this product has not

been evaluated by the PMRA, and there are currently no registered products available in North America (www.autan.co.uk/index.html).

- **Insecticides**
  - **Treated mosquito nets**: All travellers with itineraries to locales outside Canada that are endemic for malaria should be strongly encouraged to use pyrethroid (e.g., permethrin, deltamethrin, lambda-cyhalothrin, cyfluthrin, alpha-cypermethrin) insecticide-impregnated mosquito nets unless their sleeping quarters are well-screened or otherwise protected from mosquitoes (A I – evidence-based medicine recommendation). Pyrethroids may kill mosquitoes directly after they land on impregnated netting, or repel them. In either case, the end result is protection against mosquito bites and malaria. Pyrethroid-impregnated nets are significantly more effective in preventing malaria than untreated nets and are safe for children and pregnant women (A I – evidence-based medicine recommendation). The duration of efficacy of pyrethroid-impregnated nets varies from several months to 1 year, depending on the product used (Appendix III and Table 2). While pyrethroids are generally considered to be of low mammalian toxicity, care should be taken when impregnating the permethrin or equivalent product into the net: follow the label instructions, use impervious gloves, and allow the net to dry before use (Appendix III). The PMRA does not currently register pyrethroid treatments for bed nets.

Table 2.
Comparative efficacy of pyrethroid insecticides for use on nets*

Active ingredient	Formulation	Brand**	Duration of efficacy† (mos)	Level of evidence
Permethrin EC 55%	Emulsified concentrate	Peripel	6	A I
Deltamethrin SC 1%	Suspension concentrate	K-Orthrine	12	A I
Deltamethrin 400 mg	Tablet	K-O Tab	12	A I
Lambda-Cyhalothrin CS 2.5%	Capsule suspension	Icon	9	A I
Cyfluthrin EW 0.05%	Water emulsion	Solfac	6-9	A I
Alpha-Cypermethrin SC 10%	Suspension concentrate	Fendona	6-9	A I

*Based on studies of insecticide-treated mosquito nets used for the prevention of malaria in subSaharan Africa

** NOTE: These products are presented as examples only and are not necessarily endorsed by Health Canada.

†Durations of efficacy not applicable to pyrethroid impregnation of clothing; deltamethrin residual efficacy maintained after three to four washings of impregnated net whereas the efficacy of other pyrethroids is lost after one to two washings.

- **Treated clothing:** Pyrethroid treatment of clothing will also reduce the risk of malaria (Appendix III). As with mosquito net treatments, the PMRA does not currently register permethrin clothing treatments, but several products are available in the United States. These usually consist of 0.5% permethrin in an aerosol or pump spray. Treatment of clothing with the 0.5% permethrin aerosol or pump spray is generally effective at preventing mosquito bites for at least 2 weeks, assuming regular laundering practices (e.g., through six machine washings). A long-acting DEET formulation applied to exposed skin together with pyrethroid-impregnated clothing are considered to be complementary, i.e., using both will greatly enhance protection against biting arthropods (A II – evidence-based medicine recommendation).
- **Ineffective personal protective measures against insects:** There are additional products that are marketed as safe, "natural" and/or effective measures to substantially reduce the risk of mosquito bites. However, CATMAT's assessment is that the following products do not have sufficient scientific basis to recommend them, or there is sufficient scientific evidence to indicate that the product is not useful (E II – evidence-based medicine recommendation). These include electronic (ultrasonic) devices, wristbands/neckbands/anklebands impregnated with repellents (whether for animal or human use), electrocuting devices (i.e., "bug zappers"), odour-baited mosquito traps, the Citrosa plant (i.e., geranium houseplant), oral vitamin B1, and Avon Skin-So-Soft (IR3535).

c. Chemoprophylactic Drugs (where appropriate)

Recommendations for chemoprophylaxis of malaria should be based on several factors:

- individual risk assessment
- distribution of drug-resistant malaria
- safety and efficacy of chemoprophylactic regimens (see Section 3, Chemoprophylactic Regimens).

Individual risk assessment

Several factors need to be assessed when selecting an appropriate chemoprophylactic regimen before travel. The travel itinerary should be reviewed in detail and compared with known areas of malaria transmission within a country to determine the likelihood that the traveller will be at risk of acquiring malaria. The specific activities (e.g., rural travel, night-time exposure, unscreened accommodations) of the individual while in the malarial region(s) should be considered in estimating risk. The health of the individual (e.g., age, pregnancy, medication, and chronic illness) also needs to be considered in order to determine the risk of severe disease if malaria were to occur and to choose an appropriate antimalarial drug for chemoprophylaxis.

The following should be considered in the individual risk assessment:

i. Will the traveller be exposed to malaria?
ii. Will the traveller be in a drug-resistant *P. falciparum* zone?
iii. Will the traveller have prompt access to medical care (including preparation of blood films with sterile equipment and prompt, accurate interpretation) if symptoms of malaria were to occur?
iv. Are there any contraindications to the use of a particular antimalarial drug?
v. Is the traveller at increased risk of severe malaria disease, e.g., a young child, asplenic individual, pregnant woman?

Distribution of drug-resistant malaria (see Figure 1a and Appendix I)

Chloroquine-resistant *P. falciparum* is widespread in all malaria-endemic areas of the world, except for Mexico, the Caribbean, Central America (north of the Panama Canal), parts of China, and parts of the Middle East. *P. falciparum* malaria resistant to chloroquine AND mefloquine is still rare except in Thailand, on the borders with Cambodia and Myanmar (Burma). Resistance to Fansidar® (sulfadoxine-pyrimethamine) is now common in the Amazon basin, parts of subSaharan Africa and Southeast Asia. Chloroquine-resistant *P. vivax* is also an important problem, particularly in Papua New Guinea, Papua (Irian Jaya), Vanuatu, Myanmar, and Guyana. Strains of *P. vivax* with reduced response to primaquine are reported from widely divergent areas, including Papua New Guinea, Somalia, and India.

CATMAT considers there to be minimal risk of malaria in urban centres of Southeast Asia, and Central and South America. Malaria transmission falls at altitudes exceeding 2000 m (6500 feet) and is virtually non-existent over 3000 m (10 000 feet).

d. Early Diagnosis and Treatment

All travellers should be informed that malaria should be suspected if unexplained fever occurs during or after travel. Medical attention should be sought as soon as possible, and the traveller should request that a thick and thin blood film be promptly (i.e., immediately) obtained and examined for malaria parasites. If the initial blood film is negative and the traveller remains symptomatic, then the blood film should be repeated in 12 to 24 hours. The most important factors that determine the survival of patients with falciparum malaria are early diagnosis and prompt initiation of appropriate treatment.

Appendix IV provides a checklist for the preparation of travellers to malarial areas.

3. CHEMOPROPHYLACTIC REGIMENS

a. Introduction

Medications to reduce the risk of visitors acquiring clinical malaria should be considered during evening or overnight exposure in the following areas:

URBAN AND RURAL AREAS OF

(Higher risk) – subSaharan Africa (except most of South Africa) and Oceania (including Papua New Guinea, Papua, Solomon Islands and Vanuatu)

(Low to moderate risk) – Haiti, India, Bangladesh, Pakistan, and Nepal (Terai region)

RURAL AREAS OF

Southeast Asia, Central and South America, and certain parts of Mexico, North Africa, and the Dominican Republic (adjacent to Haitian border).

Travellers should be informed that antimalarial medication can markedly decrease the risk of acquiring symptomatic malaria. However, none of these agents can guarantee complete protection against malaria. Personal protective measures are an important adjunct to malaria prevention, even for those taking chemoprophylactic drugs (see Section 2, page 3, for prevention). Symptoms due to malaria may occur as early as 1 week after first exposure and as late as several years after travellers leave a malarial region whether or not chemoprophylaxis has been used. Most travellers who acquire *P. falciparum* infection will develop symptoms within 3 months of exposure. Falciparum malaria can be effectively treated early in its course, but delay in therapy may result in a serious and even fatal outcome.

FEVER OCCURRING IN A TRAVELLER WITHIN 3 MONTHS OF DEPARTURE FROM A MALARIA- ENDEMIC AREA IS A MEDICAL EMERGENCY AND SHOULD BE INVESTIGATED URGENTLY BY MEANS OF THICK AND THIN BLOOD FILMS; IF SYMPTOMS PERSIST, THESE FILMS SHOULD BE REPEATED TWICE AT 12 TO 24 HOUR INTERVALS IF THE PATIENT REMAINS SYMPTOMATIC (SEE SECTION 8 AND FIGURE 3)

There is no global consensus on malaria chemoprophylactic regimens. During their travels many individuals will encounter other travellers or health care providers who will counsel them to change or stop their antimalarial medication (especially mefloquine), leaving them at high risk of acquiring potentially life-threatening malaria. Travellers should be warned of this possibility; as well, the antimalarial guidelines and the risks and benefits of effective chemoprophylaxis should be reinforced. Appendix V (page 57), entitled "Frequently Asked Questions about Malaria", may aid the practitioner in answering travellers' questions. If desired, this text can be copied and provided to the traveller.

Table 3 summarizes the different chemoprophylactic options according to the presence of drug resistance. See Section 9 for details regarding individual chemoprophylactic agents.

b. Chloroquine-sensitive Regions

Chloroquine-sensitive regions are those malarial areas where chloroquine resistance has not been documented or is not widely present. These include Haiti, the Dominican Republic, Central America north of the Panama Canal, North Africa and parts of the Middle East, and west/central China. See individual countries in Appendix I (page 47) for precise recommendations.

Drug of choice: chloroquine (Aralen®) is the drug of choice for travellers to areas with chloroquine-sensitive malaria (A I – evidence-based medicine recommendation, see Appendix II). Chloroquine is taken once weekly, beginning 1 week before entering a chloroquine-sensitive malarial region, during the period of exposure, and for 4 weeks after leaving the malarial region.

Alternatives: For individuals unable to tolerate chloroquine, atovaquone/proguanil, doxycycline, or

mefloquine should be used (see Section 3c, and Section 9).

c. Chloroquine-resistant Regions

The chloroquine-resistant regions refer to most of Africa, South America, Oceania and Asia. See individual countries in Appendix 1 for specific recommendations. Note that some border areas of Thailand, Myanmar, and Cambodia are also mefloquine-resistant regions (see Section 3d).

There are sufficient data in semi-immune and non-immune hosts in various geographic locations to conclude that atovaquone/proguanil, doxycycline, and mefloquine are equally efficacious in the prevention of chloroquine-resistant malaria.

Drugs of choice: Atovaquone/proguanil, doxycycline, or mefloquine (A 1 – evidence-based medicine recommendation); see Table 3 and Section 9 for details on each medication.

Atovaquone/proguanil is taken daily, beginning 1 day before entering the malarial region, during the period of exposure, and for 1 week after leaving the malarial region.

Doxycycline is taken daily, beginning 1 day before entering the malarial region, during the period of exposure, and for 4 weeks after leaving the malarial region.

Mefloquine is taken weekly, beginning 1 week before entering the malarial region, during the period of exposure, and for 4 weeks after leaving the malarial region.

Alternative: primaquine is taken daily, beginning 1 day before entry into the malarial region, during the period of exposure, and for 4 weeks after leaving the malarial region.

NOTE: Primaquine is CONTRAINDICATED in G6PD (glucose-6-phosphate dehydrogenase) deficiency and CONTRAINDICATED in pregnancy. See Table 8 for details on medication.

d. Chloroquine- and Mefloquine-resistant Regions

Resistance to both chloroquine and mefloquine has been reported sporadically from various countries in Asia, Africa, and in the Amazon basin. However, it has not been found to be a significant problem except in rural, wooded regions where Thailand borders with Myanmar (Burma) and Cambodia. These are areas that are infrequently visited by tourists. See Figure 1b (page 2) for a map of this area. In addition to chemoprophylaxis, personal protective measures should be optimized.

Drug of choice: Doxycycline (see Table 3 and Section 9). Doxycycline is taken daily, beginning 1 day before entering the malarial region, during the period of exposure, and for 4 weeks after leaving the malarial region.

Alternatives: There are no trials of alternative prophylactic agents for travellers to this region. Therefore unnecessary travel to the area, especially by pregnant women and children < 8 years of age, should be avoided. Atovaquone/proguanil has been a successful treatment for multi-drug resistant malaria in Thailand, and therefore this medication may be considered for travellers at risk in whom doxycycline is contraindicated or not tolerated. Atovaquone/proguanil is taken daily, beginning 1 day before entering the malarial region, during the period of exposure, and for 1 week after leaving the malarial region.

Table 3.
Malaria chemoprophylaxis regimens for at-risk individuals[a] according to presence of drug resistance

Region	Drug(s) of choice[b]	Alternatives
Chloroquine sensitive	Chloroquine	Atovaquone/proguanil, doxycycline, mefloquine
Chloroquine resistant	Atovaquone/proguanil, doxycycline, or mefloquine	Primaquine[c]
Chloroquine and mefloquine resistant	Doxycycline[d]	Atovaquone/proguanil

[a]IMPORTANT NOTE: Protection from mosquito bites (bed nets, insect repellents, etc) is the first line of defence against malaria for **ALL** travellers. In the Americas and Southeast Asia, chemoprophylaxis is recommended ONLY for travellers who will be exposed outdoors in rural areas during evening or night-time.

[b]See text and Table 8 for adult and pediatric dosing information.

[c]Contraindicated in G6PD (glucose-6-phosphate dehydrogenase) deficiency and in pregnancy.

[d]Contraindicated in pregnancy, during breast-feeding, and in children < 8 years.

e. Primaquine Terminal Prophylaxis for Prevention of Relapses of *P. vivax* and *P. ovale*

P. vivax and *P. ovale* parasites can persist in the liver and cause relapses for as long as 5 years after routine chemoprophylaxis has been discontinued. Since most malarial areas of the world (except Haiti and the Dominican Republic) have at least one species of relapsing malaria, travellers to these areas have some risk of acquiring either *P. vivax* or *P. ovale*, although actual risk for an individual traveller is difficult to define. Primaquine decreases the risk of relapses by acting against the persistent liver stages (hypnozoites) of *P. vivax* and *P. ovale*. Primaquine terminal prophylaxis is administered after the traveller has left a malaria-endemic area, usually during or after the last 2 weeks of chemoprophylaxis. It is generally indicated only for people who have had prolonged exposure in malaria-endemic regions (e.g., long-term travellers or expatriates). Primaquine is contraindicated in pregnant women and individuals deficient in G6PD (see Table 3 and Section 9).

f. Selection of Antimalarial Drugs for Individual Travellers

Malaria causes severe illness that may be life-threatening. Mortality is at least 1% and increases to 20% or more in severe or complicated cases. Therefore it is *always* preferable to prevent the disease rather than treat someone after symptoms develop. Given the variety of choices in medication, a traveller at risk of malaria should always be encouraged to use chemoprophylaxis along with personal protective measures against insect bites (see Section 2).

All antimalarial drugs have the potential to cause side effects and should be prescribed only after completion of an individual risk assessment (as outlined in Section 2, page 8), to ensure that only travellers truly at risk of malaria infection receive antimalarial chemoprophylaxis. In deciding between the various chemoprophylactic options, the health care provider must weigh the traveller's underlying health status, other medications, malaria drug efficacy, risks and character of adverse drug reactions as well as the individual's preference against the likelihood that he or she will be exposed to malaria.

Most users of antimalarial chemoprophylaxis will have no or only minor adverse reactions. However, preconceived ideas about side effects may profoundly influence the traveller's confidence in a particular medication option and should be considered in the selection process. If adverse events do occur, they can have a significant impact not only on the traveller's health but also on his or her compliance with the medication. One option available is a trial of medication in advance of travel to test for tolerability. To keep adverse effects to a minimum, it is essential that all travellers be educated about the dosing schedule, including time of day and association with food, as

well as precautions regarding sun exposure or other advice, depending on the drug used. Remember that while several antimalarial drugs may be equally efficacious when studied in clinical trials, their effectiveness is a measure of protection offered in real life. The more educated and compliant the patient, the closer the effectiveness is to the efficacy of a given chemoprophylactic agent.

Fatal malaria has occurred in travellers who have discontinued an effective antimalarial drug in favour of one that is less protective. Therefore, travellers should be warned to continue their malaria chemoprophylaxis regardless of what they are told by other travellers. Different medications used in other areas of the world may be less effective or associated with serious adverse effects, and are not recommended. Examples include proguanil alone (Paludrine®), pyrimethamine (Daraprim®), dapsone/pyrimethamine (Maloprim®), and mefloquine/sulfadoxine-pyrimethamine (Fansimef®).

SUMMARY POINTS TO KEEP IN MIND DURING THE DISCUSSION OF CHEMOPROPHYLAXIS INCLUDE THE FOLLOWING:

1. Inform patients that malaria can kill, but medications rarely cause serious adverse events if selected and used with care.
2. Select a medication that is least likely to exacerbate any past or present medical problems.
3. Indicate that medication should be taken in the recommended fashion to minimize significant side effects.
4. Discuss the option of a drug trial before the trip to check tolerability, if this is a concern.
5. Discuss strategies to change medication if serious adverse effects should arise during the trip.
6. Do not try to talk someone into a particular medication choice if there are alternatives that are considered to be just as efficacious.
7. Recommend that, if a malaria medication is tolerated well, the traveller should continue taking it regardless of what others say.

4. PREVENTION OF MALARIA IN SPECIAL HOSTS

a. Malaria Prevention in Children

Travellers should be clearly advised of the risks involved in taking young children to areas with drug-resistant falciparum malaria. Children are at special risk of malaria, since they may rapidly become seriously ill. In order to reduce the risk of infection when travel to malarial areas is unavoidable, all children, including those who are breast-fed, should be well protected against mosquito bites and receive appropriate malaria chemoprophylaxis.

Protection from bites should include alteration of the itinerary to limit time spent in malarial regions as well as to avoid outdoor activities after dusk. Pyrethroid-treated netting may be used for more than just beds (e.g., over strollers, playpens, and cradles) to protect the very young from bites. For ALL children travelling to malarial regions, particular attention should be paid to other personal protective measures, such as protective and treated clothing as well as effective insect repellents (see Section 2). These recommendations may differ from common practices in other areas of the world, such as Canada, where serious insect-borne disease is less of a concern.

All infants and children should be prescribed an appropriate antimalarial drug if they are at risk of infection. Infants do not receive sufficient medication through breast milk to protect them, and therefore they should be prescribed antimalarial drugs even though their mother is receiving chemoprophylactic medication. Ensuring that young children take antimalarial agents may be difficult because of the lack of pediatric formulations and the unpleasant taste. Malaria tablets may be crushed and mixed with chocolate syrup, jam, cereal, or bananas to mask the taste. Sufficient tablets should be prescribed to allow for a few doses that may be vomited or spat out. Emesis is more frequent among children, and therefore parents must be given clear instructions as to when doses should be repeated. For small doses, the pharmacist may be asked to pre-cut tablets in order to increase the accuracy of dosing and/or crush and insert into capsules. Parents must be aware that antimalarial drugs should be protected from sunlight and high humidity. As with all medication, they should be kept out of reach of infants and children and stored in childproof containers to avoid a potential fatal overdose.

Chloroquine remains the preferred agent for chemoprophylaxis in areas with chloroquine-sensitive malaria. Although it is not available in Canada, chloroquine sulfate (for example, Nivaquine) is widely available as a syrup in malaria-endemic areas. The syrup is often more easily administered than tablets. Physicians should calculate the dose to be administered according to body weight, as the volume will vary with the different concentrations of chloroquine base that may be found in suspensions available abroad.

Mefloquine is the drug of choice in chloroquine-resistant regions, although there are no studies that specifically analyze its bioavailability and rate of metabolism in children. Although the manufacturer recommends that mefloquine not be given to children weighing < 5 kg, it should be considered for prophylaxis of all children at high risk of acquiring chloroquine-resistant *P. falciparum*, at a dose of 5 mg base/kg once weekly (see Section 9, Table 8, page 43). Young children seem to be less likely to suffer major neuropsychiatric side effects from mefloquine.

Atovaquone/proguanil has been licensed for the treatment of malaria in children > 11 kg (25 lb) or aged > 3 years. However, it is available in many countries for use in this age group for both treatment and prophylaxis, and its safety is supported by clinical trials; in the United States atovaquone/proguanil can be used for the treatment of malaria in children weighing > 5 kg (11 lb) (A 1 – evidence-based medicine recommenda-

tion, see Appendix II). Currently, it is licensed in Canada for prophylaxis in those weighing > 40 kg. Doxycycline can be used in children > 8 years of age, with attention to contraindications and precautions.

There is no safe and effective chemoprophylactic regimen licensed for children < 8 years who travel to mefloquine-resistant areas where Thailand borders with Myanmar (Burma) and Cambodia, in western Cambodia, and eastern Myanmar. However, as in adults, atovaquone/proguanil may be considered on the basis of its documented efficacy when used as treatment for malaria in these regions.

Recommendations

i. If possible, young children should avoid travel to areas with significant transmission particularly of chloroquine-resistant malaria (C III – evidence-based medicine recommendation).

ii. Personal protective measures should be strongly encouraged for all children who travel to malaria-endemic areas (A I – evidence-based medicine recommendation).

iii. Young children travelling to or residing in chloroquine-sensitive areas should use chloroquine as chemoprophylaxis (A I – evidence-based medicine recommendation).

iv. For young children travelling to or residing in chloroquine-resistant areas, mefloquine is the drug of choice for chemoprophylaxis (A I – evidence-based medicine recommendation). An alternative is atovaquone/proguanil, although it is not licensed in Canada for this use.

v. There is no safe and effective chemoprophylaxis regimen licensed for children < 8 years old who travel to mefloquine-resistant areas where Thailand borders with Cambodia and Myanmar (Burma), although atovaquone/proguanil may be considered.

b. Malaria Prevention in Pregnancy

Malaria increases the risk of maternal and neonatal death, miscarriage, and stillbirth. In addition, low birth weight is more frequent among women who are taking ineffective prophylaxis (A I – evidence-based medicine). Pregnant women should defer travel to malaria-endemic areas, particularly to areas with risk of acquisition of drug-resistant falciparum malaria. If travel cannot be avoided, special care should be taken to avoid mosquito bites (see Section 2), and chemoprophylaxis should be used.

Doxycycline is contraindicated for malaria prophylaxis during pregnancy and lactation because of adverse effects on the fetus, including discoloration and dysplasia of the teeth, and inhibition of bone growth. Primaquine is contraindicated during pregnancy because the drug can be passed transplacentally to a G6PD-deficient fetus and cause hemolytic anemia in utero. Whenever radical cure or terminal prophylaxis with primaquine is indicated during pregnancy, chloroquine should be given once a week until delivery, at which time primaquine may be given. Atovaquone/proguanil is not currently recommended during pregnancy unless the potential benefit outweighs the potential risk to the fetus (for example, for a pregnant woman who is at significant risk of acquiring *P. falciparum* malaria in an area of multidrug-resistant strains).

According to current data, mefloquine is safe for chemoprophylaxis after the first trimester, with no evidence of increased teratogenic effects. Although study results are conflicting, some suggest that there may be an increased rate of spontaneous abortion, particularly during the first trimester. It is prudent to recommend avoidance of pregnancy for 3 months after completion of mefloquine chemoprophylaxis because of the long half-life. However, if a woman who is receiving mefloquine prophylaxis becomes

pregnant this is not an indication for termination of pregnancy. If there is an unavoidable risk of chloroquine-resistant malaria during the first trimester of pregnancy, the risks of malaria to the mother and fetus should be weighed against the small risks associated with mefloquine. Chloroquine and proguanil are known to be safe in pregnancy, although they are significantly less effective than mefloquine in preventing chloroquine-resistant *P. falciparum*.

Recommendations

i. If possible, pregnant women should avoid travel to areas with significant transmission particularly of chloroquine-resistant malaria (C III – evidence-based medicine recommendation).

ii. Personal protective measures should be strongly encouraged for all pregnant women who travel to malaria-endemic areas (A I – evidence-based medicine recommendation).

iii. Pregnant women travelling to or residing in chloroquine-sensitive areas should use chloroquine as chemoprophylaxis (A I – evidence-based medicine recommendation).

iv. Mefloquine is effective and safe for prophylaxis beyond the first trimester of pregnancy and is recommended where exposure to chloroquine-resistant falciparum malaria is unavoidable (AI – evidence-based medicine recommendation).

v. Women who plan to travel to areas with chloroquine-resistant falciparum malaria during the first trimester of pregnancy should have an individual risk assessment and counsel from a travel medicine or tropical diseases specialist (A III – evidence-based medicine recommendation).

vi. The combination of chloroquine and proguanil is safe in pregnancy but is significantly less effective against chloroquine-resistant malaria than mefloquine. In view of the serious consequences of malaria in pregnancy, utilization of this suboptimal antimalarial combination would **not** routinely be recommended (A I – evidence-based medicine recommendation).

vii. There is no safe and effective licensed chemoprophylaxis regimen for pregnant women who travel to mefloquine-resistant areas where Thailand borders with Cambodia and Myanmar (Burma).

c. Prophylaxis while Breast-feeding

Because the quantity of antimalarial medication transferred in breast milk is insufficient to provide adequate protection against malaria, infants who require chemoprophylaxis should receive the recommended dosages of appropriate antimalarial drugs. The very small amount of chloroquine, mefloquine, and proguanil secreted in the breast milk of lactating women is not thought to be harmful to a nursing infant. There is no information on the amount of primaquine that enters human breast milk; therefore, the infant should be tested for G6PD deficiency before primaquine is given to a woman who is breast-feeding. Because data are not yet available on the safety and efficacy of atovaquone/proguanil in infants weighing < 11 kg (25 lbs), the medication should not be given to a woman who is breast-feeding an infant less than this weight unless the potential benefit to the woman outweighs the potential risk to the infant (for example, a lactating woman who has acquired *P. falciparum* malaria in an area of multidrug-resistant strains and who cannot tolerate other treatment options).

d. Malaria Prevention in the Medically Compromised Host

Travellers with underlying medical conditions present a special challenge, for a wide variety of reasons. These include the potential for increased susceptibility to and severity of malaria, the deleterious impact of malaria on the underlying condition, and the com-

plexity of potential interactions between antimalarial and other medications.

Immunocompromised hosts

i. **HIV/AIDS**: Early studies of the interaction between HIV and *P. falciparum* resulted in conflicting conclusions but were limited by poor design or the small numbers of subjects. More recent data suggest a two-way relation between these two organisms. *In vitro* and human data indicate that malaria infection stimulates HIV-1 replication, resulting in increased viral loads that persist for weeks after the infection. Thus, malaria may speed the clinical progression of HIV disease. It has also been shown that infants born to co-infected women have a higher mortality rate than those born to women with either HIV/AIDS or malaria alone. Conversely, a recent, well-designed study has shown that those infected with HIV have an increased risk of *Plasmodium* parasitemia and clinical malaria infection. Infection risk and parasite density increase as the immune status deteriorates (A I – evidence-based medicine). Malaria treatment failure may be more likely in those with HIV/AIDS, as shown in Ugandan children < 5 years of age.

   Treatment of HIV often includes multiple antiretroviral drugs, several of which (especially protease inhibitors) may interact with antimalarial drugs or cause adverse effects. The result may be increased toxic effects from or reduced efficacy of either the antiretroviral agent or the antimalarial medication. Consultation with a travel or tropical medicine expert is advised.

ii. **Asplenia:** The spleen facilitates phagocytosis and promotes removal of parasitized red blood cells. Animal models suggest that asplenia exacerbates malaria disease. Fatal malaria has been reported in those with asplenia, although it may be more important in non-immune (e.g., travellers) than semi-immune populations. It is presumed that *Plasmodia* species cause more severe disease in travellers with functional or anatomic asplenia and, therefore, maximal preventive measures should be recommended. Standby self-treatment may be considered in addition to prophylactic measures if remote regions are being visited, where access to care is limited. Fever in an asplenic individual may represent malaria or infection with an encapsulated bacterial organism, so empiric therapy for both may need to be instituted (B III – evidence-based medicine recommendation).

iii. **Other immunosuppressive conditions:** Little has been documented about the natural history of malaria in individuals with other immunocompromising conditions. The clinical course of malaria in these individuals is presumably similar to or worse than in other people. However, the practitioner should also consider any immunosuppressive medications that are being used, many of which are metabolized in the liver by the microsomal enzymes and thus may interact with certain antimalarial medications.

Other Conditions

i. **Cardiovascular:** Mefloquine is contraindicated in those with cardiac arrhythmias or conditions that may predispose to arrhythmia. Doxycycline should not be used in patients taking warfarin because of potentiation of the latter's effect. There is a single case report of possible interaction between proguanil and warfarin, therefore a trial of atovaquone/proguanil with testing of INR (International Normalized Ratio) may be prudent until more information becomes available.

ii. **Neuropsychiatric**: Seizure disorders may be exacerbated by chloroquine and mefloquine, so alternative agents should be used. Febrile seizures in children are not thought to be a risk factor or contraindication for these drugs. Concurrent use of anti-convulsant drugs that are liver-metabolized may decrease serum levels of doxycycline, and a dosage adjustment is recommended (see Section 3f). Mefloquine is associated with exacerbation of psychiatric conditions, including depression and anxiety disorders, and should be avoided if these illnesses are identified.

iii. **Hepatic or renal dysfunction:** Moderate to severe hepatic or renal dysfunction may result in significant alteration in antimalarial medication

levels. If either the liver or kidneys are compromised, then there must be careful consideration given to the selection and dosing of medications for the prophylaxis and treatment of malaria. Consultation with a travel or tropical medicine specialist is recommended.

Recommendations

i. Consultation with a travel medicine or tropical disease specialist is advised for anyone with a significant medical condition or immunosuppression (B III – evidence-based medicine recommendation).

ii. All compromised travellers must be made aware of their degree of risk and should review the necessity of the trip along with options to alter the itinerary and their behaviour to reduce malaria risk as much as possible (B III – evidence-based medicine recommendation).

iii. Personal protective measures for malaria prevention must be emphasized (A III – evidence-based medicine recommendation).

iv. Carefully selected antimalarial chemoprophylaxis should be used for those at unavoidable risk of the disease (A I – evidence-based medicine recommendation).

v. In compromised travellers at high risk of severe disease, the option of standby self-treatment with malaria medication should be discussed. This should be offered in addition to chemoprophylaxis for use in case of fever if the traveller is going to be in a remote area or an area where safe and effective care is not promptly available. Broad spectrum antibiotics are also important in asplenic patients, since infections with bacteria and *Plasmodia* may be indistinguishable and sometimes co-exist (B III – evidence-based medicine recommendation).

5. MALARIA PREVENTION IN THE LONG-TERM TRAVELLER OR EXPATRIATE

Modern prevention strategies have had a significant, positive impact on the risk of mortality in long-term expatriates, which was reported to be as high as 60% among missionaries in West Africa during the 19th century. However, the effort to develop unique, evidence-based guidelines for the long-term (> 6 months) traveller or expatriate is severely hampered by a paucity of medical literature in this area.

Concerns encountered when addressing malaria prevention in long-term travellers and expatriates include conflicting counsel regarding appropriate chemoprophylaxis and self-treatment, the safety of drugs used for chemoprophylaxis, fear of toxic effects with prolonged use of medication, and lack of adherence to the use of personal protective measures. Confidence but lack of rigour in self-diagnosis coupled with unreliable laboratory diagnosis in many developing countries have resulted in a misrepresentation of drug efficacy by the long-term traveller/expatriate.

Data on the incidence of malaria and the effectiveness and tolerance of currently recommended regimens for long-term travellers are limited to the studies of Peace Corps volunteers, in whom mefloquine was well tolerated and was more effective than chloroquine and proguanil in chloroquine-resistant regions. At present, there is no evidence that long-term use of therapies currently recommended for short-stay travellers causes significant adverse reactions. Doxycycline may be an exception, as studies have been confined to short-term travellers and people using tetracyclines (at lower doses) as therapy for skin conditions. In general, guidelines for the prevention of malaria in long-term travellers or expatriates should not deviate significantly from standard recommendations for the short-term traveller.

A recent, self-reported summary of the malaria prevention strategies of 1192 long-term expatriates, representing a broad range of government and non-government organizations in subSaharan Africa, may provide some assistance in counselling long-term travellers and expatriates. Overall, their compliance rate was approximately 60%. Of those receiving chemoprophylaxis, 54% reported changing their prophylactic regimen, 22% because of adverse effects. The severity of the adverse effects was not associated with any specific drug, but the reported incidence of neuropsychiatric side effects was 10% among people taking chloroquine and proguanil as compared with 17% in the mefloquine group. Mefloquine was the only regimen for which participants reported a change in practice based on media influence. Only a small number indicated that availability and cost were factors in their choice of prophylactic regimen. Participants who did not use prophylaxis cited concerns about adverse reactions and long-term effects as the primary reasons for their choice. Personal protective measures were suboptimal: only 38% had screened doors and windows, and 53% used mosquito netting (20% of which were insecticide-treated nets).

There are no data available on self-diagnosis and self-treatment of malaria in the long-term traveller or expatriate population. Without training, there is no reason to believe that the efficacy of these interventions will be any better than that demonstrated in the general travel population. However, given that long-term travellers and expatriates represent a reasonably homogeneous group, training in diagnosis and self-treatment (see Sections 6 and 7), including the use of rapid diagnostic tests for malaria, may

prove to be helpful in this population when access to reliable, formal medical care is inadequate. Self-diagnostic kits that require refrigeration will limit access to this technology in some regions.

Section 3e (page 12) addresses the use of primaquine as terminal prophylaxis to decrease the risk of relapses through its action against the liver stages of *P. vivax* and *P. ovale*. Primaquine terminal prophylaxis is administered after the traveller has left a malaria-endemic area, usually during or after the last 2 weeks of chemoprophylaxis. Terminal prophylaxis with primaquine is generally indicated only for people who have had prolonged exposure in malaria-endemic regions, such as expatriates or long-term travellers. Primaquine is contraindicated in pregnant women and individuals deficient in G6PD (see Section 9 for contraindications and precautions).

In conclusion, guidelines for the prevention of malaria in long-term travellers or expatriates should not deviate significantly from the recommendations for short-term travellers (B III – evidence-based medicine recommendation, see Appendix II). The available data indicate that expatriates in high-risk settings have not effectively used personal protective measures (B II – evidence-based medicine). The majority use a prophylactic regimen, but sound counsel does not always guide their choice: a significant proportion is influenced by perception of risk rather than documented problems. Thus the effectiveness of current recommendations will be influenced by the prevailing attitudes in the subculture in which the long-term traveller or expatriate lives (C – evidence-based medicine). At present, there is insufficient evidence for the effectiveness of self-diagnosis with rapid malaria test kits to recommend their routine use. Primaquine should be given as terminal prophylaxis, after consideration of precautions and contraindications, to long-term travellers or expatriates who return from regions with *P. vivax* transmission (A I – evidence-based recommendation).

6. SELF-TREATMENT OF PRESUMPTIVE MALARIA

Counsel regarding appropriate management of malaria is of value for all travellers in regions where malaria is highly endemic because reliable medical attention may not be available. However, travellers to high-risk regions should never rely exclusively on a self-treatment regimen. Under some circumstances, individuals at risk of malaria may be unable to seek medical care within 24 hours and may not have access to facilities that stock appropriate medications; therefore, they require access to medication for self-treatment of presumptive malaria.

All travellers should be advised that the signs and symptoms of malaria are non-specific, that there is a risk of other potentially serious illnesses mimicking malaria, and that there are potential adverse reactions to malaria therapy; thus self-treatment should never be undertaken lightly. Consultation with a tropical medicine expert is recommended before individuals are advised to embark on a self-treatment program.

Training long-term travellers and expatriates to become proficient in their practice of self-treatment is difficult, and efforts should focus on those living in areas where access to expert supervision and care of high quality is limited, and where the threat of malaria is significant. Ninety percent of global episodes of clinical malaria and deaths occur in subSaharan Africa; therefore, particular attention should be given to people travelling to that region.

Training should consist of the following steps:

Step 1 – Discuss Common Errors Concerning Malaria Recognition and Management

The consultant should discuss common errors that have compromised the value of self-treatment:

- Expatriates assume that they can recognize malaria from the symptoms.
- They do not consistently assume that fever is malaria until proven otherwise.
- They commonly mistake the anti-inflammatory and antipyretic effect of chloroquine to signify that they have successfully treated malaria.
- They do not always choose an appropriate regimen –
  - the drug administered for treatment is the same as that used for prevention;
  - single drug therapy is chosen over combination therapy;
  - the dose used is often that used in the community for "semi-immunes";
  - the drug used is often less effective than that used for prevention, e.g., mefloquine for prevention, chloroquine for treatment.

Step 2 – Advise that Malaria Presents in Various Ways

Travellers should be advised that the clinical presentation of malaria is variable and may mimic other diseases. An alternative diagnosis that requires treatment may be present, particularly in travellers who have been compliant with an appropriate chemoprophylaxis regimen. The most frequent symptoms of malaria are fever, headache, and generalized aches and pains. Fever, which may or may not be cyclical, is almost always present. Malaria can be misdiagnosed as influenza or another febrile illness, so that an early and accurate diagnosis is essential. Malaria is likely to be over-reported by laboratory technicians; nevertheless, if malaria is diagnosed there should be follow-up with medical management.

Step 3 – Indicate the Need to Seek Professional Medical Care as Soon as Possible

Travellers should be told that self-treatment is NOT considered definitive treatment but is a temporary, life-saving measure while they seek medical attention. Self-treatment for malaria should be undertaken only if fever develops and professional medical care is not available within 24 hours. After self-treatment, medical attention should still be sought as soon as possible.

Step 4 – Select the Self-treatment Drug with Care

When choosing a drug regimen for self-treatment, safety, efficacy, and drug tolerance must be considered priorities. Individuals who are undergoing chemosuppression should never attempt treatment with the same drug, as there is the potential for additive toxicity and reduced efficacy.

Recommended Regimens

(NOTE: to be used only if fever develops and medical care is not available within 24 hours)

1. For individuals in chloroquine-sensitive regions who are not receiving chloroquine prophylaxis:
   a. Self-treatment with chloroquine should be initiated (see Table 4, page 24).
   b. SEEK MEDICAL HELP AS SOON AS POSSIBLE.
   c. Chloroquine prophylaxis should be started.
2. For individuals in chloroquine-sensitive regions who are already receiving chloroquine prophylaxis:
   a. Self-treatment with atovaquone/proguanil should be initiated (see Table 4).
   b. SEEK MEDICAL HELP AS SOON AS POSSIBLE.
   c. Chloroquine prophylaxis should be resumed.
3. For individuals in chloroquine- or chloroquine- and mefloquine-resistant *P. falciparum* regions who are not receiving atovaquone/proguanil chemoprophylaxis:
   a. Self-treatment with atovaquone/proguanil OR quinine plus doxycycline should be initiated.
   b. SEEK MEDICAL HELP AS SOON AS POSSIBLE.
   c. Atovaquone/proguanil, doxycycline, or mefloquine should be started or resumed.
4. For individuals in chloroquine- or chloroquine- and mefloquine-resistant *P. falciparum* regions who are receiving atovaquone/proguanil chemoprophylaxis:
   a. Self-treatment with quinine plus doxycycline should be initiated.
   b. SEEK MEDICAL HELP AS SOON AS POSSIBLE.
   c. Atovaquone/proguanil should be resumed.

Travellers may not have access to drugs approved by Health Canada when travelling in chloroquine- or chloroquine- and mefloquine-resistant regions. Conversely, they may have access to medication endorsed by the Roll Back Malaria Program that has not been formally approved for use in Canada. The Roll Back Malaria Program advocates the use of some fixed combination therapies because they improve compliance and efficacy while reducing errors and the emergence of drug resistance (see Table 4).

Step 5 – Educate About Drugs to Avoid

Warn the traveller about the following drug regimens, which are no longer recommended for self-treatment because of potential severe adverse effects and/or poor efficacy:

- Halofantrine (causes cardiac deaths)
- Mefloquine (unacceptably high rates of severe adverse events at treatment doses)
- Fansidar® alone (sulfadoxine plus pyrimethamine) (resistance)
- Fansimef® (mefloquine plus Fansidar®) (resistance)
- Chloroquine plus Fansidar® (resistance, ineffective)

Rapid detection of malaria using a simple dipstick test may be available to some travellers. The sensitivity and specificity of these tests vary, from 50% to 90%. Furthermore, there are limited data about their accuracy in the hands of non-experienced operators and under non-refrigerated conditions in the tropics. There are no rapid detection kits currently licensed in North America (see Section 7).

Table 4. Drugs for the self-treatment of malaria

Drug, generic (trade) name	Adult dosage	Pediatric dosage	Advantage	Disadvantage	Adverse effects	Health Canada approval status
Chloroquine (Aralen®) Tablet: 150 mg base	1.5 g base over 3 days 600 mg base, then 300 mg base in 6 hours, then 300 mg base daily x 2 days	**Treatment:** 25 mg base/kg total over 3 days 10 mg base/kg, then 5 mg base/kg in 6 hours, then 5 mg base/kg daily x 2 days	Safe in pregnancy Safe for children Long-term safety data	Widespread resistance Should not be administered to people using chloroquine for prevention	**Frequent:** nausea, emesis, headache **Occasional:** skin eruptions **Rare:** nerve deafness, photophobia, myopathy, blood dyscrasias, psychosis and seizures	Approved by Health Canada for treatment of chloroquine-sensitive malaria (Central America and Haiti) Not recommended for self-treatment in other regions because of risk of mixed infection with *P. falciparum*
Atovaquone/proguanil (Malarone®) Adult tablet: 250 mg atovaquone plus 100 mg proguanil	1000 mg atovaquone AND 400 mg proguanil (4 tablets) once daily x 3 days	20 mg/kg atovaquone AND 8 mg/kg proguanil daily x 3 days 11-20 kg: 1 tablet daily 21-30 kg: 2 tablets daily 31-40 kg: 3 tablets daily ≥ 41 kg: 4 tablets daily	Safe for children > 5 kg Resistance rare Fixed combination allows for simple treatment regimen Excellent safety profile	Not approved in pregnant women or breast-feeding mothers Contraindicated in presence of renal failure (creatinine clearance < 30 mL/min) Nausea and vomiting common with malaria and as side effect of medication Emesis may interfere with success of treatment May need to premedicate with Gravol	**Frequent:** nausea, vomiting, abdominal pain, diarrhea, increased transaminase levels **Rare:** seizures, rash	Approved by Health Canada for treatment of chloroquine- resistant malaria
Quinine sulfate PLUS Doxycycline	Quinine 250 mg base, 2 tablets three times daily x 7 days Doxycyline 100 mg twice daily x 7 days	Quinine 7.5 mg base/kg three times daily x 7 days Doxycycline 1.5 mg/kg twice daily x 7 days < 25 kg or < 8 yrs: contraindicated 25-35 kg or > 8 yr: 50 mg bid 36-50 kg: 75 mg bid > 50 kg: adult dose	Resistance to combined therapy rare Rapid parasite clearance Readily available Cheap	Children < 8 yr cannot receive doxycycline Contraindicated in pregnancy Complicated regimen reduces compliance Adverse reactions to quinine common and interfere with tolerance and effectiveness	**Frequent:** Cinchonism (tinnitus, nausea, headache, blurred vision), hypoglycemia, nausea, emesis **Occasional:** hypersensitivity, nerve deafness, esophageal ulcer (doxycycline) **Rare:** hemolysis	Approved by Health Canada for treatment of chloroquine- resistant malaria

Drug, generic (trade) name	Adult dosage	Pediatric dosage	Advantage	Disadvantage	Adverse effects	Health Canada approval status
Co-artemether Coartem™ Riamet™ Novartis	Artemether 20 mg AND Lumefantrine 120 mg 6 dose regimen standard for non-immune travellers at 0 and 8 hours on day 1 and twice daily on days 2 and 3 **4 tablets per dose**	Artemether 20 mg AND Lumefantrine 120 mg 6 dose regimen standard for non-immune travellers at 0 and 8 hours on day 1 and twice daily on days 2 and 3 **5 kg to < 15 kg: 1 tab/dose** **15 to 24 kg: 2 tabs/dose** **25 to 34 kg: 3 tabs/dose** **≥ 35 kg: 4 tabs per dose**	Safety profile from data available suggests safe for children > 5 kg Resistance not documented Rapid parasite clearance Drug widely distributed in Africa More readily available and less expensive than Malarone® Better tolerated than artesunate plus mefloquine No adjustment of dose required for elderly and renal failure Lumefantrine does not cause cardiac conduction disturbance	Not in pregnant women and breast-feeding mothers Two regimens (4 dose and 6 dose) described on product monograph is confusing; NOTE: the 4 dose regimen for **semi-immunes** only	**Frequent:** nausea, vomiting, abdominal pain, fatigue **Occasional:** fever, rigors, anemia (some adverse events reported may be due to malaria)	**Not approved by Health Canada but endorsed by WHO (Roll Back Malaria Program)**

7. MALARIA DIAGNOSIS

It is imperative that a travel history be obtained from all patients with a history of fever, and that thick and thin blood films for malaria be requested urgently for all individuals who have travelled to or through a malaria-endemic area. *P. falciparum* malaria usually presents within 3 months of last exposure; however, it may be delayed in patients who have taken chemoprophylaxis. In addition, other types of malaria, especially that caused by *P. vivax*, may occur months and occasionally up to 5 years after travel in endemic areas.

The treatment of malaria depends upon the species of parasite and the level of parasitemia; therefore, every effort should be made to determine these parameters on an urgent basis. Since malaria is a reportable disease in all provinces/territories, physicians are required to report all cases to the local public health authority.

Occasionally, a single blood film examination may be falsely negative for malaria parasites. Repeat blood films over 48 hours (e.g., every 12 hours x 3) may be required to exclude the possibility of malaria.

The examination of thick and thin blood films by an experienced microscopist is essential for the diagnosis of malaria. The clinical presentation (history and physical examination) of malaria is often non-specific. When malaria is a consideration, especially when the patient may be at risk of *P. falciparum* infection (whether chloroquine-sensitive or not), the laboratory diagnosis and quantification of the level of parasitemia must be considered a medical emergency and performed as soon as possible (< 24-hour turnaround time).

Not all laboratories are proficient in the diagnosis and speciation of malaria. If appropriate expertise cannot be ensured, then the patient should be treated empirically for chloroquine-resistant falciparum malaria and an immediate referral of the patient or the specimen should be made to a specialized facility. These facilities can be identified through the Canadian Malaria Network Centres, listed in Appendix VI.

While rapid diagnostic tests (RDTs) that use dipstick techniques for the diagnosis of malaria are currently being evaluated in the research setting, none is currently licensed for use in Canada. These RDTs are based on antigen detection of trophozoites and are targeted primarily at *P. falciparum* infections. Some tests differentiate between infections with other species or between falciparum and non-falciparum infection. They are simple to perform and do not require special equipment. They are rapid to interpret and require minimal training to operate. On the other hand, they may remain positive for up to 2 weeks after microscopic clearance, they are relatively expensive compared with microscopy, and they are not quantitative.

A WHO working group has reviewed the issues surrounding these test kits and identified further research required and possible scenarios for their use. One such scenario would be for self-treatment by travellers to remote areas. Research to date would suggest that this is not feasible, as interpretation by lay people is inaccurate (D II – evidence-based medicine, see Appendix II). There are no data available on self-diagnosis and self-treatment in the long-term traveller or expatriate population. Without training, there is no reason to believe that the efficacy of these interventions will be any better than that demonstrated in the general travel population. However, given that long-term travellers and expatriates represent a reasonably homogeneous group, training in diagnosis and self-treatment (see Section 6), including the use of rapid diagnostic tests for malaria, may prove to be helpful in this population when access to reliable, formal medical care is inadequate. Self-diagnostic kits that require refrigeration will limit access to this technology in some regions.

Polymerase chain reaction (PCR) techniques are also rapidly emerging as a definitive diagnostic tool and

can demonstrate impressive sensitivity and specificity (B I – evidence-based medicine). They are, however, limited to laboratories that have the expertise and equipment to conduct these analyses and are still primarily research tools. They are useful as an adjunct to microscopy to confirm cases with low parasitemia and uncertain species. This is particularly useful in Canada, where the incidence of disease is quite low. The Canadian Malaria Network Centres, identified in Appendix VI, can direct clinicians to sites where this technology is available.

Recommendations

i. The diagnosis of malaria in a suspected case is a medical emergency and requires accurate laboratory testing within a maximum of 24 hours (A I – evidence-based medicine).

ii. Microscopy of Giemsa stained thick and thin smears is the current gold standard for the laboratory diagnosis of malaria (A I – evidence-based medicine). Wright's stained thick and thin smears are used in some laboratories but may miss parasite details that assist in speciation.

iii. PCR has a role in the confirmation of diagnosis but is not accessible widely in a timely fashion, as of yet.

iv. RDTs are of limited utility in the Canadian setting and should not be used as a primary diagnostic tool (DI – evidence-based medicine).

8. TREATMENT OF MALARIA

Malaria, particularly that due to *P falciparum*, is a medical emergency, and management includes immediate treatment and close follow-up. If the species is not unequivocally identified, the case should be treated as *P. falciparum* until further identification and, if there is doubt about resistance patterns, *P. falciparum* should be treated as chloroquine resistant. In Canada, all patients with malaria due to *P. falciparum* should be considered for admission to hospital or should receive initial treatment in an observation unit to ensure tolerance of treatment and to confirm decreasing parasitemia with treatment. Severe or complicated disease (see Table 5) requires parenteral therapy and close clinical monitoring, preferably in an intensive care unit. If required, assistance in the management of malaria cases can be obtained through access to the Canadian Malaria Network site in the appropriate area (a contact list is available in Appendix VI).

a. General Principles of Management

The initial management of the patient depends on many factors, including the infecting species of malaria, the severity of infection, the patient's age, the pattern of drug resistance in the area of acquisition as well as the safety, availability, and cost of antimalarial drugs. The base-salt equivalents of selected antimalarials are shown in Table 6.

Three questions need to be addressed in order to initiate effective treatment:

1. **Is this infection caused by *P. falciparum*?**

This is critical, as treatment varies according to the species of malaria.

2. **Is this a severe or complicated infection (see Table 5)?**

Severe or complicated malaria requires parenteral therapy and sometimes an exchange transfusion.

Table 5. Criteria for severe falciparum malaria

EITHER

History of recent possible exposure and no other recognized pathology

OR

Asexual forms of *P. falciparum* on blood smear

AND

Any one or more of the following 11 features:

1) Impaired consciousness or coma
2) Severe normocytic anemia
3) Renal failure
4) Pulmonary edema or adult respiratory distress syndrome (ARDS)
5) Hypoglycemia
6) Circulatory collapse, shock
7) Spontaneous bleeding/disseminated intravascular coagulation
8) Repeated generalized convulsions
9) Acidemia/acidosis
10) Hemoglobinuria
11) Parasitemia of > 5% (> 250 000/microlitre) in non-immune individuals

Adapted from *Management of Severe Malaria: A Practical Handbook*. 2nd ed. Geneva: World Health Organization, 2000.

3. **Has the infection been acquired in an area of known drug-resistant malaria (see Appendix 1)?**

Therapy will have to be modified accordingly. *When in doubt, treat all falciparum malaria as drug resistant.*

Treatment of malaria does not stop with selection of appropriate antimalarial medications. For all cases of malaria, medical follow-up must be ensured. Clinical assessment and repeat malaria smears should be carried out daily until negative and again 7 and 28 days after treatment, and at any time symptoms recur.

Table 6. Base/salt equivalents of selected antimalarial drugs

Drug	Base (mg)	Salt (mg)
Chloroquine phosphate	150.0	250.0
Chloroquine sulfate[a]	100.0	136.0
Clindamycin hydrochloride	150.0	225.0
Mefloquine	250.0	274.0
Quinidine gluconate	5.0 7.5 10.0 15.0	8.0 12.0 16.0 24.0
Quinidine sulfate[b]	7.5 10.0 15.0	9.0 12.0 18.0
Quinine dihydrochloride	5.0 7.5 15.0 16.7	6.0 9.0 18.0 20.0
Quinine sulfate	250.0	300.0

[a]Not available in Canada
[b]Intramuscular preparation should not be used intravenously.

b. Management of Falciparum Malaria

The following guidelines have been derived, in part, from the WHO Division of Control of Tropical Diseases (*Management of Severe Malaria: A Practical Handbook*. 2nd ed. Geneva: World Health Organization, 2000). The interested reader is referred to this document for a more detailed discussion of these issues.

- A detailed geographic history is essential to the management of malaria. *P. falciparum* malaria acquired in areas where drug resistance is known to occur should be treated as chloroquine resistant.
- As a general rule, all non-immune patients with *P. falciparum* malaria, whether severe or not, should be considered for admission to hospital in order to ensure tolerance of antimalarial drugs and to detect complications or early treatment failure. If hospital admission is not planned, then all cases must be observed during their first dose of therapy to ensure that it has been tolerated before discharge from the emergency department. Before discharge there must be further treatment doses provided, or the patient should be directed to a pharmacy that can fill the prescription appropriately.
- An algorithm for the management of malaria is presented in Figure 3.

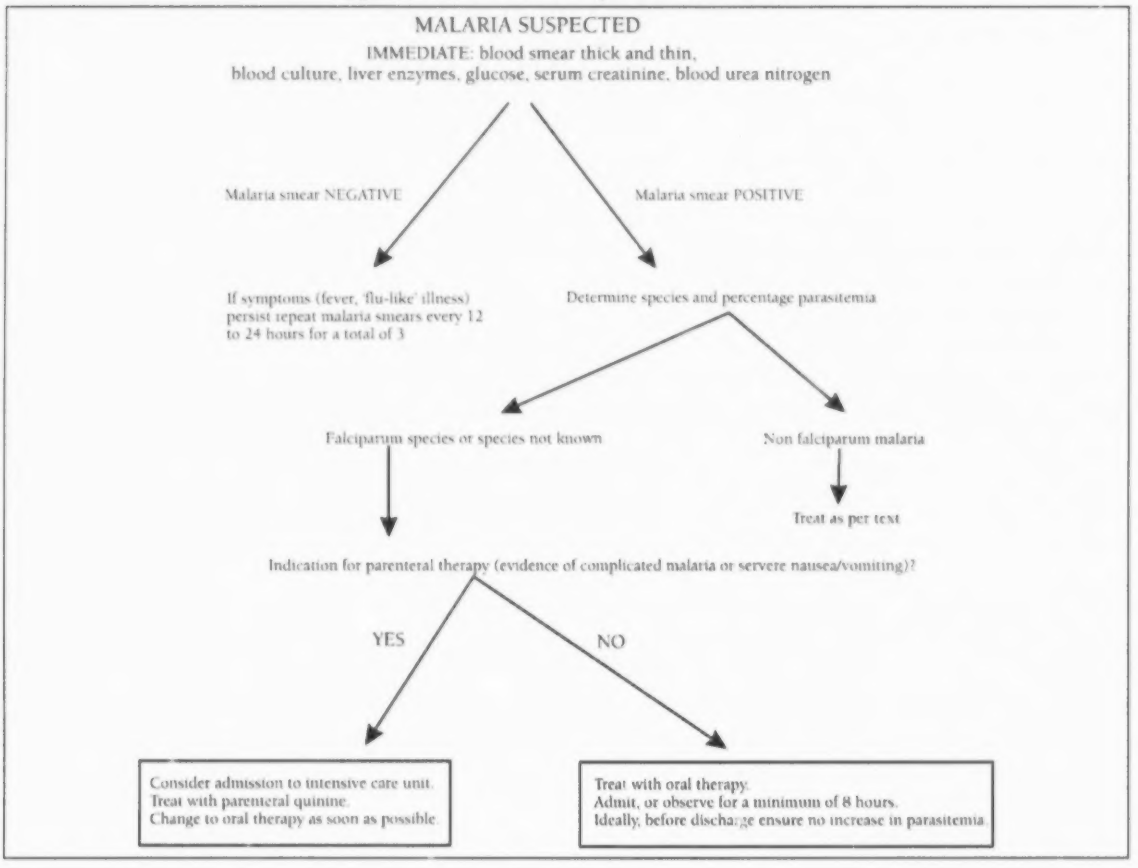
Severe P. falciparum

Severe *P. falciparum* infections, as defined by the criteria in Table 5, may have a mortality rate of 20% or higher. Patients with these infections require immediate hospitalization and urgent, intensive medical management. They are at risk of all the adverse outcomes defined in Table 5 as well as other adverse outcomes, including permanent neurologic deficits, chronic renal insufficiency, and death.

All patients with severe *P. falciparum* infections and those who are unable to tolerate drugs orally should receive intravenous quinine (see Table 7) available 24 hours per day via the Canadian Malaria Network (see Appendix VI for more information). Less optimally, they can be treated with parenteral quinidine. CATMAT prefers quinine because of the cardiotoxicity of quinidine, necessitating electrocardiographic monitoring and dose reduction with cardiac toxic effects (infusion rates should be decreased if the corrected QT interval is prolonged by more than 25% of baseline). When quinine or quinidine is administered to a patient who has taken mefloquine or halofantrine in the previous 2 weeks, there is a risk of drug-induced cardiac arrhythmia; such patients should be monitored electrocardiographically.

Many ancillary treatments have been suggested for the treatment of severe malaria, but few have been objectively shown to improve outcome. Only antipyretic drugs (acetaminophen) and anticonvulsants (prophylactic phenobarbitol) have been supported by sufficient evidence to warrant their use. The use of steroids to treat severe or cerebral malaria has been associated with worse outcomes and should be avoided (E I – evidence-based medicine recommendation, see Appendix II). In cases of complicated *P. falciparum* infection (Table 5), or if there is high parasitemia (> 10%), exchange transfusion has been used on an experimental basis as a

Figure 3
Algorithm for the management of malaria


MALARIA SUSPECTED
IMMEDIATE: blood smear thick and thin,
blood culture, liver enzymes, glucose, serum creatinine, blood urea nitrogen
Malaria smear NEGATIVE
Malaria smear POSITIVE
If symptoms (fever, 'flu-like' illness) persist repeat malaria smears every 12 to 24 hours for a total of 3
Determine species and percentage parasitemia
Falciparum species or species not known
Non falciparum malaria
Treat as per text
Indication for parenteral therapy (evidence of complicated malaria or servere nausea/vomiting)?
YES
NO
Consider admission to intensive care unit.
Treat with parenteral quinine.
Change to oral therapy as soon as possible.
Treat with oral therapy.
Admit, or observe for a minimum of 8 hours.
Ideally, before discharge ensure no increase in parasitemia.

potentially life-saving procedure. When managing a patient with severe or complicated falciparum malaria, consultation with an infectious or tropical disease expert is strongly recommended (see Appendix VI for contact information).

Uncomplicated P. falciparum

Uncomplicated cases of *P. falciparum* can become severe over 12 to 24 hours if not treated and monitored properly. Infections unequivocally acquired in a chloroquine-sensitive zone may be treated with chloroquine alone (as per Table 8, page 43). Infections possibly or definitely acquired in drug-resistant regions (most cases of *P. falciparum* malaria seen in Canada) should be treated with atovaquone/proguanil or quinine plus a second drug (preferably doxycycline). If the patient can tolerate quinine given orally, then it and the second drug – either doxycycline or, for those in whom doxycycline is contraindicated, clindamycin – may be administered simultaneously or sequentially (start quinine first). If oral medication cannot be tolerated, then parenteral quinine should be administered as per Table 7.

c. Management of Non-falciparum Malaria (*P. vivax, P. ovale, P. malariae*)

Outside of New Guinea (Papua New Guinea and Papua [Irian Jaya]), chloroquine remains the treatment of choice for malaria other than falciparum malaria (as per Table 8). As with *P. falciparum* malaria, response to treatment should be documented

with a repeat of thick and thin blood films on day 7 and day 28 after therapy, and at any time there is recurrence of symptoms. A recurrence of parasitemia < 30 days after treatment suggests chloroquine-resistant *P. vivax*; recurrence after ≥ 30 days suggests primaquine resistance.

Recent reports have confirmed the presence and high prevalence (80%) of chloroquine-resistant *P. vivax* in Papua (Irian Jaya). Sporadic cases of chloroquine-resistant *P. vivax* malaria have been reported elsewhere (e.g., in Indonesia, Papua New Guinea, the Solomon Islands, Myanmar, and Guyana). At present, chloroquine can no longer be relied upon either for chemoprophylaxis or treatment of *P. vivax* acquired in New Guinea, and the optimal treatment is unknown. Although effective, a prolonged course of quinine (> 3 days) is often required to cure *P. vivax* infection from New Guinea, and it is poorly tolerated. Mefloquine and halofantrine have been shown to be efficacious in small clinical trials, but each is limited by safety issues associated with therapeutic doses. Standard chloroquine doses (25 mg base/kg every 72 hours) combined with high-dose primaquine (2.5 mg base/kg every 48 hours) have been suggested as treatment for chloroquine-resistant *P. vivax* acquired in Irian Jaya but have failed in cases from Guyana. Expert advice from an infectious or tropical disease specialist should be sought for the management of these cases (see contact information, Appendix VI).

P. vivax and *P. ovale* have a persistent liver phase that is responsible for relapses and is susceptible only to treatment with primaquine or related drugs. Relapses caused by the persistent liver forms may appear months and, rarely, up to 5 years after exposure. None of the currently recommended chemoprophylaxis regimens will prevent relapses due to these two species of Plasmodium. In order to reduce the risk of relapse following the treatment of symptomatic *P. vivax* or *P. ovale* infection, primaquine is indicated to provide "radical cure".

The possibility of G6PD deficiency should be excluded before antirelapse therapy with primaquine is given. In patients with known or suspected G6PD deficiency, expert medical advice should be sought, since primaquine may cause hemolysis in such patients. Primaquine use is contraindicated in pregnancy. *P. vivax* or *P. ovale* infections occurring during pregnancy should be treated with standard doses of chloroquine (Table 8). Relapses can be prevented by weekly chemoprophylaxis with chloroquine until after delivery, when primaquine can be safely used for mothers with normal G6PD levels.

Primaquine is not routinely recommended to prevent relapsing malaria in asymptomatic returning travellers (terminal prophylaxis). However, it is generally indicated for people with prolonged exposure in malaria-endemic areas where vivax or ovale malaria occurs (e.g., long-term travellers or expatriates, see Section 5). For terminal prophylaxis, primaquine is administered after the traveller has departed from a malaria-endemic area, usually during or after the last 2 weeks of chemoprophylaxis (see Section 3 and Table 8 for dosage recommendations).

P. vivax isolates with a decreased responsiveness to primaquine are well documented in Southeast Asia and, in particular, Papua New Guinea and Irian Jaya. Recently, primaquine radical treatment failure has been reported from Thailand and Somalia. Therefore, the recommended dosage of primaquine to prevent relapse has increased to 30 mg (0.5 mg/kg) daily for 14 days.

When *P. vivax* malaria relapses after primaquine therapy there are two issues to be considered: (1) the treatment of the acute vivax malaria (see Table 8), and (2) prevention of further relapses by a doubling of the standard dose of primaquine, i.e., 30 mg (0.5 mg/kg) of primaquine base daily for 14 days (B1 – evidence-based medicine recommendation).

Blood infection with *P. malariae* may persist for many years, but it is not life-threatening and is easily cured by a standard treatment course of chloroquine (see Table 8).

Table 7. Chemotherapy of severe OR complicated *P. falciparum* malaria

NOTE: A switch to oral therapy should be made as soon as possible.

A. If an infusion pump is available:

Quinine[a] (base) 5.8 mg/kg loading dose (quinine dihydrochloride[b] [salt] 7 mg/kg) intravenously by infusion pump **over 30 minutes** followed immediately by **8.3 mg base/kg** (quinine dihydrochloride [salt] 10 mg/kg) diluted in 10 mL/kg isotonic fluid by intravenous infusion over 4 hours (maintenance dose), repeated 8 hourly[c] until the patient can swallow, then quinine tablets to complete 3 to 7 days of treatment (7 days for SE Asia).

B. Without an infusion pump:

Quinine[a] (base) 16.7 mg/kg loading dose, (quinine dihydrochloride[b] [salt] 20 mg/kg), by intravenous infusion **over 4 hours**, then **8.3 mg base/kg** (quinine dihydrochloride [salt] 10 mg/kg) diluted in 10 mL/kg isotonic fluid by intravenous infusion over 4 hours (maintenance dose), repeated 8 hourly[c] until the patient can swallow, then quinine tablets to complete 3 to 7 days of treatment (7 days for SE Asia).

PLUS (either concurrently with quinine or immediately after)

1. Doxycycline: 100 mg orally twice daily for 7 days; pediatric dose = 2 mg/kg (to a maximum of 100 mg) twice daily; contraindicated: pregnancy, breast-feeding or if age < 8 years.

OR

2. Atovaquone/proguanil: 4 tablets once daily for three days (see Table 8 for pediatric dosage).

OR

3. Clindamycin: 10 mg/kg (loading dose) intravenously, followed by 5 mg/kg every 8 hours until blood is clear of sexual parasites (Note: Should be used only if patient is unable to take doxycycline or atovaquone/proguanil).

Note: Parenteral quinidine should be used only if parenteral quinine is unavailable. Because of increased risk of cardiac toxic effects with quinidine, cardiac monitoring is required. Parenteral quinidine gluconate may be obtained on a patient-by-patient basis with authorization from the Special Access Programme, Therapeutic Products Directorate, Finance Building, 2nd Floor, Tunney's Pasture, Ottawa, Ontario K1A 1B9, Address Locator 0202C1, (613) 941-2108 (08:30-16:30 hours EST), (613) 941-3061 (after hours), (613) 941-3194 (fax), Web site: www.hc-sc.gc/hpb-dgps/therapeut

[a] Loading dose should **not** be used if patient received quinine, quinidine, or mefloquine within the preceding 24 hours.

[b] Parenteral quinine dihydrochloride may be obtained through the Canadian Malaria Network (see Appendix VI for contact information).

[c] Switch to oral therapy with quinine as soon as possible. In patients requiring > 48 hours of parenteral therapy, reduce the quinine maintenance dose by one-third to one-half.

9. DRUGS FOR THE PREVENTION AND TREATMENT OF MALARIA

Travellers should be reminded that antimalarials, like all drugs, have the potential to cause adverse effects. These drugs should be prescribed after an individual risk assessment (as outlined in Section 2) to ensure that only those travellers truly at risk of malaria infection receive antimalarial chemoprophylaxis. Any drugs taken for chemoprophylaxis should be used in conjunction with personal protective methods to prevent mosquito bites (see Section 2). Most people using antimalarial chemoprophylaxis will have no or only minor adverse reactions, which can be minimized by careful adherence to dosing guidelines, precautions, and contraindications.

This chapter will review the drugs (in alphabetical order) used for the prevention (chemoprophylaxis) and treatment of malaria. This information is not designed to be comprehensive. It is important to note that product recommendations are subject to change, and therefore providers should consult up-to-date information, including recent drug monographs, for any updates, particularly with respect to compatibility, adverse reactions, contraindications, and precautions. Further details and discussion on recommendations concerning the use of these drugs for chemoprophylaxis and treatment can be found in Sections 3 and 8 respectively. Table 8 summarizes information, including doses, for the antimalarial drugs routinely used in Canada.

Figure 4 depicts the malaria lifecycle and the sites of action of recommended chemoprophylactic drugs.

ATOVAQUONE/PROGUANIL (ATQ/PG)

Trade Name: Malarone®. Licensed in Canada for malaria chemoprophylaxis in adults weighing > 40 kg and for treatment of uncomplicated malaria in adults and children.

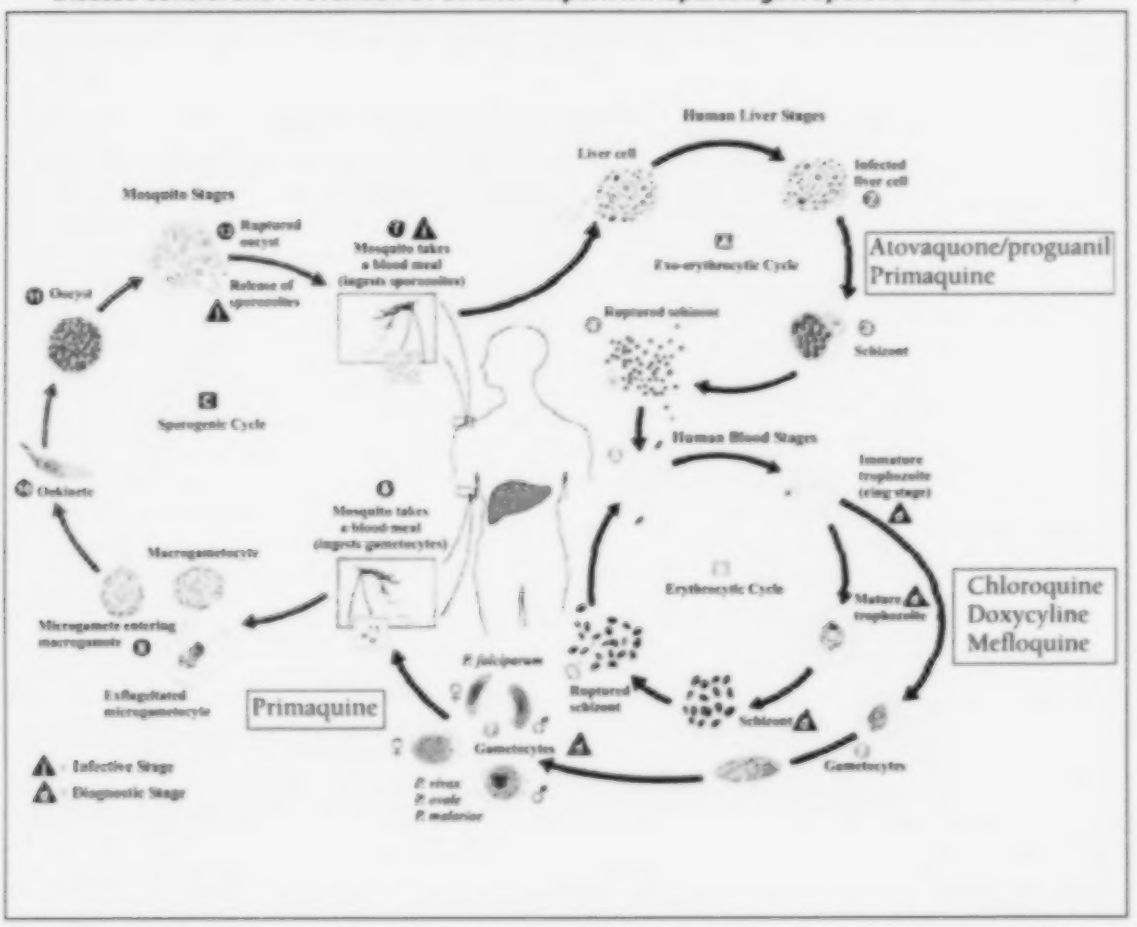
Mechanism of Action: Atovaquone/proguanil is a fixed drug combination of atovaquone 250 mg and proguanil 100 mg, in a single tablet. The two components are synergistic, atovaquone inhibiting parasite mitochondria and proguanil, along with its active metabolite cycloguanil, causing inhibition of parasite folate synthesis through effects on dihydrofolate reductase. Atovaquone/proguanil is effective as a causal (acting at the liver stage) as well as suppressive (acting at the blood stage) prophylactic agent. Atovaquone/proguanil must be taken DAILY. Because of the causal effects, atovaquone/proguanil can be discontinued 1 week after departure from a malaria-endemic area.

Indications and Efficacy: For malaria chemoprophylaxis, atovaquone/proguanil has equal efficacy (i.e., > 95%) to doxycycline and mefloquine against chloroquine-resistant falciparum malaria (A I evidence-based medicine); it is also effective along the borders of Thailand, where chloroquine and mefloquine resistance is documented.

In clinical trials of treatment of acute, uncomplicated *P. falciparum* malaria conducted in Southeast Asia, South America, and Africa, the efficacy of the combination of atovaquone/proguanil (dosed once daily for 3 days) has exceeded 95%. As well, published case reports have documented that it successfully treated multidrug-resistant malaria that had failed to respond to other therapies (AI – evidence-based medicine recommendation, see Appendix II). Therefore, atovaquone/proguanil, an effective and well-tolerated therapy, is considered first-line treatment of noncomplicated *P. falciparum* infection, including multidrug-resistant *P. falciparum* (A I – evidence-based medicine recommendation.

There is insufficient evidence at this time to recommend atovaquone/proguanil for the routine treatment of non-falciparum malaria, although limited data suggest efficacy for the treatment of *P. vivax* (C – evidence-based medicine).

Figure 4. Malaria life cycle and primary areas of drug activity (modified from the U.S. Centers for Disease Control and Prevention DPDx site: http://www.dpd.cdc.gov/dpdx/html.Malaria.htm)



The malaria parasite life cycle involves two hosts. During a blood meal, a malaria-infected female Anopheles mosquito inoculates sporozoites into the human host❶. Sporozoites infect liver cells❷ and mature into schizonts❸, which rupture and release merozoites❹. (Of note, in *P. vivax* and *P. ovale* a dormant stage [hypnozoites] can persist in the liver and cause relapses by invading the bloodstream weeks or even years later.) After this initial replication in the liver (exo-erythrocytic schizogony A), the parasites undergo asexual multiplication in the erythrocytes (erythrocytic schizogony B). Merozoites infect red blood cells❺. The ring stage trophozoites mature into schizonts, which rupture releasing merozoites❻. Some parasites differentiate into sexual erythrocytic stages (gametocytes)❼. Blood stage parasites are responsible for the clinical manifestations of the disease.

Daily atovaquone/proguanil can now be considered as first-line chemoprophylaxis for travellers to areas with multi-drug resistant falciparum malaria (with attention to contraindications and precautions) (A I – evidence-based medicine recommendation).

Adverse Effects, Contraindications and Precautions: Compared with other standard antimalarial regimens, the atovaquone/proguanil combination for chemoprophylaxis has demonstrated excellent safety and tolerance. During treatment, the most frequent adverse events are those associated with the gastrointestinal tract: approximately 8% to 15% of adults and children experience nausea, vomiting, abdominal pain, or diarrhea, and 5% to 10% develop transient, asymptomatic elevations in transaminase and amylase levels. Serious adverse events associated with atovaquone/proguanil, such as seizure and rash, are rare. Atovaquone has been associated with fever and rash in HIV-infected patients, requiring discontinuation of therapy, and has been shown to be teratogenic in rabbits but not in rat models (Food and Drug Administration category C drug). Proguanil is well tolerated, and although oral aphthous ulcerations are not uncommon they are rarely severe enough to warrant discontinuing this medication.

Pregnancy, severe renal insufficiency (creatinine clearance < 30 mL/min) and hypersensitivity to either component are the only contraindications to atovaquone/proguanil.

AZITHROMYCIN

Trade Name: Zithromax™

Mechanism of Action: Azithromycin is a macrolide antibiotic that inhibits parasite protein synthesis.

Indications and Efficacy: Azithromycin has not been shown to be very effective in the prevention of malaria (AII – evidence-based medicine). Studies performed to date are small and suggest that azithromycin is less effective than atovaquone/proguanil, doxycycline, mefloquine, or primaquine. Azithromycin, which must be taken daily, should be considered for chemoprophylaxis only in very selective groups.

There is insufficient evidence to recommend azithromycin as an alternative antimalarial except under circumstances in which other, more effective and safer, medications are not available or are contraindicated (CI – evidence-based medicine recommendation).

Adverse Effects, Contraindications and Precautions: Azithromycin is considered to be safe in pregnancy and for children, and is available in suspension. However, in view of the serious consequences of malaria in pregnancy, use of this suboptimal antimalarial would not routinely be recommended.

CHLOROQUINE

Trade Name: Aralen®

Mechanism of Action: Chloroquine is a synthetic 4-aminoquinoline, which acts against the intraerythrocytic stage of parasite development. It interferes with the digestion of hemoglobin within the red cell and leads to toxic metabolite formation within the parasite's food vacuole.

Indications and Efficacy: Chloroquine, taken once weekly, is effective for malaria prevention and treatment in travellers to areas with chloroquine-sensitive malaria (A I – evidence-based medicine recommendation). It remains the drug of choice for malaria chemoprophylaxis of travellers to areas with chloroquine-sensitive malaria and the drug of choice for the treatment of chloroquine-sensitive falciparum malaria, chloroquine sensitive *P. vivax* as well as *P. ovale* and *P. malariae* infections. Chloroquine is suitable for people of all ages and for pregnant women. There is insufficient drug excretion in breast milk to protect a breast-feeding infant, and therefore nursing infants should be given chloroquine (adjusted for changing weight, see Table 8). Since overdoses are frequently fatal, instructions for childhood doses should be carefully followed, and the medication should be kept out of the reach of children.

Weekly chloroquine plus daily proguanil is approximately 60% more efficacious in subSaharan Africa than weekly chloroquine alone, but it is much less efficacious than atovaquone/proguanil, doxycycline

or mefloquine (A I – evidence-based medicine recommendation) and is **not** routinely recommended for Canadian travellers.

Adverse Effects, Contraindications and Precautions: Except for its bitter taste, chloroquine is usually well tolerated. Taking the drug with food may reduce other mild side effects, such as nausea and headache. Black-skinned people may experience generalized pruritus, which is not indicative of drug allergy. Transient, minor visual blurring may occur initially but should not be a reason to discontinue chloroquine. Retinal toxic effects, which may occur with long-term daily doses of chloroquine (> 100 g total dose) used in the treatment of other diseases, is extremely unlikely with chloroquine given as a weekly chemoprophylaxis. Chloroquine may worsen psoriasis and, rarely, is associated with seizures and psychosis. Therefore, chloroquine should not be used in individuals with a history of epilepsy or generalized psoriasis (C III – evidence-based medicine recommendation). Concurrent use of chloroquine interferes with antibody response to intradermal human diploid cell rabies vaccine.

CLINDAMYCIN

Trade Name: Dalacin C®

Mechanism of Action: Clindamycin is an antibiotic that inhibits parasite protein synthesis.

Indications and Efficacy: Clindamycin is indicated only for treatment of malaria in restricted circumstances. Clindamycin, although less effective than doxycycline or atovaquone/proguanil, is used in combination with quinine for those unable to tolerate or who have contraindications (e.g., pregnant women and young children) to the use of first-line agents.

Adverse Effects, Contraindications and Precautions: The most frequent adverse events with clindamycin are diarrhea and rash. *Clostridium difficile* associated disease, including pseudomembranous colitis, has been reported.

DOXYCYCLINE

Trade Name: Vibra-Tabs™

Mechanism of Action: Doxycycline is an antibiotic that inhibits parasite protein synthesis.

Indications and Efficacy: Doxycycline is effective for the prevention and treatment of chloroquine-resistant *P. falciparum*. It has been shown to have equivalent efficacy to atovaquone/proguanil and mefloquine for the prevention of chloroquine-resistant *P. falciparum* (A I – evidence-based medicine). Doxycycline is an efficacious chemoprophylactic agent against mefloquine-sensitive and mefloquine-resistant *P. falciparum* malaria (A I – evidence-based medicine recommendation) but must be taken DAILY to work. The major reason for doxycycline failures is non-compliance with this daily regimen.

Adverse Effects, Contraindications and Precautions: Doxycycline may cause gastrointestinal upset and, rarely, esophageal ulceration, which are less likely to occur if the drug is taken with food and large amounts of fluid. It should not be taken simultaneously with Pepto-bismol® or antacids. Because doxycycline is photosensitizing, it may make the skin burn more easily; use of a sunscreen that blocks ultraviolet A rays may reduce this problem. Doxycycline may also increase the risk of vaginal candidiasis; therefore, women should carry antifungal therapy for self-treatment of vaginal candidiasis. Although tetracyclines and other antibiotics have been cited as a cause of oral contraceptive failure, a recent case-control analysis failed to demonstrate any significant association. Concurrent use of doxycycline with barbiturates, carbamazapine, or phenytoin may result in a 50% decrease in doxycycline serum concentration because of induction of microsomal enzyme activity and resulting reduction of the half-life of doxycycline. Adjustment of doxycycline dosage may be necessary, using either a twice daily dosing schedule (100 mg bid) or a single dose of 200 mg daily.

Doxycycline is **contraindicated** during pregnancy, in breast-feeding women, and in children < 8 years of age. Although the long-term safety (> 3 months) of doxycycline has not been established, historically, tetracycline derivatives have been used at lower doses over many years for skin disorders.

MEFLOQUINE

Trade Name: Lariam®

Mechanism of Action: Mefloquine is a quinoline-methanol. It is a lipophylic drug that acts on the intraerythrocytic asexual stages of parasite development causing degradation of hemozoin within the food vacuole.

Indications and Efficacy: Mefloquine is an effective chemoprophylactic and therapeutic agent against drug-resistant *P. falciparum*. In Canada, it is routinely recommended **ONLY** for chemoprophylaxis because of the high rate of adverse effects with treatment doses. It is one of the drugs of choice, along with atovaquone/proguanil and doxycycline, for the prevention of malaria in travellers to chloroquine-resistant regions (A I – evidence-based medicine recommendation).

There is no evidence that toxic metabolites of mefloquine accumulate, and long-term use of mefloquine (> 1 year) by Peace Corps volunteers in Africa has not been associated with additional adverse effects. It is recommended, therefore, that the duration of use of mefloquine **NOT** be arbitrarily restricted in individuals who tolerate this medication and are at risk of acquiring malaria (B II – evidence-based medicine recommendation).

For travellers who will be at immediate high risk of drug-resistant falciparum malaria, consideration may be given to the use of a loading dose of mefloquine. Data from several trials indicate that mefloquine taken once daily for 3 days before travel followed by a once weekly dose is a well-tolerated and effective way to rapidly achieve therapeutic blood levels (reaching steady state levels in 4 days compared with 7 to 9 weeks with standard weekly dosing of mefloquine) (A I – evidence-based medicine recommendation). In controlled studies only about 1% to 2% of loading dose recipients discontinued mefloquine, and most of these did so during the first week. The loading dose strategy also permits an assessment of drug tolerance before travel and allows a change to a suitable alternative if required. Alternatively, if time permits, mefloquine may be initiated up to 3 weeks before travel in order to assess tolerance and achieve higher blood levels before the traveller enters malaria-endemic areas.

Adverse Effects: Mefloquine is generally well tolerated when used for chemoprophylaxis. Approximately 20% to 30% of travellers will experience side effects from either mefloquine or chloroquine; most of these are mild and self-limiting. The most frequent minor side effects reported with mefloquine use are nausea, strange vivid dreams, dizziness, mood changes, insomnia, headache, and diarrhea. Approximately 1% to 4% of mefloquine users may have to discontinue prophylaxis because of adverse effects, a rate not significantly different from other chemoprophylaxis regimens. Over 13 million travellers have used mefloquine prophylaxis, and severe reactions (seizure, psychosis) to this drug are rare (reported from 1 in 10,000 to 1 in 13,000 users). The great majority of mefloquine users (95% to 99%) have either no side effects or only mild and temporary ones. Occasionally, a traveller (in particular, women) will experience a less severe but still troublesome neuropsychological reaction (e.g., anxiety, mood change) to mefloquine (1 in 250 to 500 users), requiring a change to an alternative drug. These reactions are almost always reversible. On occasions, neuropsychological complaints have persisted long after mefloquine has been stopped. Rare cases of suicidal ideation and suicide have been reported, though no relation to drug administration has been confirmed.

When mefloquine is prescribed for prophylactic use, individuals should be advised that if they experience psychiatric symptoms such as acute anxiety, depression, restlessness, or confusion, these may be prodromal to more serious adverse events. They should report these adverse events immediately, the drug should be discontinued, and an alternative medication should be substituted.

CATMAT does not routinely recommend mefloquine for the treatment of malaria, because in treatment doses (25 mg base/kg) it is less well tolerated. Severe neuropsychiatric reactions are reported to be 10 to 60 times more frequent, occurring in 1/215 to 1/1,700 users of treatment doses of mefloquine.

Contraindications: These include known hypersensitivity or past severe reaction to mefloquine; history of serious psychiatric disorder (e.g., psychosis, severe depression, generalized anxiety disorder, schizophrenia or other major psychiatric disorders); and seizure disorder.

Precautions: Precautions for the use of mefloquine include use in children < 5 kg ; use in those with occupations requiring fine coordination or activities in which vertigo may be life-threatening, such as flying an aircraft; concurrent use of chloroquine or quinine-like drugs (halofantrine and mefloquine should not be used concurrently, see Section 9); underlying cardiac conduction disturbances or arrhythmia; and first trimester of pregnancy.

There have been concerns regarding the co-administration of mefloquine and agents known to alter cardiac conduction, including beta-blockers, calcium channel blockers, phenothiazines, non-sedating antihistamines, and tricyclic antidepressants. However, at present these concerns remain theoretical, and the concurrent use of these agents is not contraindicated. A recent review of available data suggests that mefloquine may be used in people concurrently taking beta-blockers if they have no underlying cardiac arrhythmia.

Insufficient mefloquine is excreted in breast milk to protect a nursing infant. Although the package insert recommends that mefloquine not be given to children weighing < 5 kg, it should be considered for children at high risk of acquiring chloroquine-resistant *P. falciparum* malaria. There are no pharmacokinetic data upon which to recommend a correct dose for children weighing < 15 kg. The WHO has suggested a chemosuppressive dose of 5 mg base/kg weekly for children weighing > 5 kg.

PRIMAQUINE

Trade Name: Primaquine (primaquine phosphate)

Mechanism of Action: Primaquine is an 8-aminoquinoline antimalarial that is active against multiple life cycle stages of the plasmodia that infect humans and has been used for over 50 years. Its mechanism of action is incompletely understood. However, it has activity against the developing liver stages (causal effect) thereby preventing establishment of infection; against liver hypnozoites, preventing relapses in established *P. vivax* and *P. ovale* infections; against blood stages; and against gametes, thereby preventing transmission.

Indications and Efficacy: Evidence is accumulating that primaquine is an effective chemosuppressive for *P. falciparum* malaria (A 1 – evidence-based medicine recommendation). Recent studies have shown efficacy in semi-immune and non-immune subjects, although data for travellers and for varied geographic regions are limited. Given at a dose of 0.5 mg/kg base per day (adult dose 30 mg base per day) for 11 to 50 weeks, primaquine had a protective efficacy of 85% to 95% against both *P. falciparum* and *P. vivax* infections. Primaquine was better tolerated than other standard chemoprophylactic regimens in people who were not G6PD deficient. Because of the causal effects of primaquine, it can be discontinued 1 week after departure from a malaria-endemic area. All travellers need to be evaluated for G6PD deficiency before

primaquine is initiated. This significantly complicates the prescription process.

P. vivax and *P. ovale* parasites can persist in the liver and cause relapses for as long as 5 years after routine chemoprophylaxis has been discontinued. Since most malarial areas of the world (except Haiti and the Dominican Republic) have at least one species of relapsing malaria, travellers to these areas have some risk of acquiring either *P. vivax* or *P. ovale*, although actual risk for an individual traveller is difficult to define. Primaquine decreases the risk of relapses by acting against the liver stages of *P. vivax* and *P. ovale*. Primaquine terminal prophylaxis is administered after the traveller has left a malaria endemic area, usually during or after the last 2 weeks of chemoprophylaxis. Terminal prophylaxis with primaquine is generally indicated only for people who have had prolonged exposure in malaria- endemic regions (e.g., long-term travellers or expatriates).

None of the other currently recommended chemoprophylaxis regimens will prevent relapses due to *P. vivax* and *P. ovale*. In order to reduce the risk of relapse following the treatment of symptomatic *P. vivax* or *P. ovale* infection, primaquine is indicated to provide "radical cure". Primaquine should be initiated for radical cure after chloroquine therapy has been completed and the acute febrile illness is over (about 1 to 2 weeks).

P. vivax isolates with a decreased responsiveness to primaquine are well documented in Southeast Asia and, in particular, Papua New Guinea and Irian Jaya. Recently, primaquine radical treatment failure has been reported from Thailand and Somalia. On the basis of increasing numbers of reports of resistance to primaquine at the standard dose of 0.25 mg/kg, the recommended dose has been increased to 30 mg (0.5 mg/kg) of primaquine base daily for 14 days (B1 – evidence-based medicine recommendation).

Although not a first-line chemoprophylactic agent, primaquine may be considered an alternative chemoprophylactic agent (with attention to contraindications and precautions) for those without G6PD deficiency when other regimens are either inappropriate or contraindicated (A1 – evidence-based medicine recommendation).

Adverse Effects, Contraindications and Precautions: Primaquine is generally well tolerated but may cause nausea and abdominal pain, which can be decreased by taking the drug with food. More importantly, primaquine may cause oxidant-induced hemolytic anemia with methemoglobinemia, particularly among individuals with G6PD deficiency, which is more common in those of Mediterranean, African, and Asian ethnic origin. As well, those receiving > 15 mg base/day have a greater risk of hemolysis. Therefore, ALL individuals should have their G6PD level measured before primaquine therapy is initiated.

Primaquine is contraindicated in patients with severe G6PD deficiencies. In mild variants of G6PD deficiency, primaquine has been used safely at a lower dose for radical cure to prevent *P. vivax* and *P. ovale* relapses (0.8 mg base/kg weekly; adult dose 45 mg base weekly for 8 weeks); however, this reduced dose is insufficient for chemoprophylactic activity. When used at prophylactic doses (0.5 mg base/kg daily) in children and men with normal G6PD activity, mean methemoglobin rates (5.8%) were below those associated with toxicity (> 10%). Patients should be advised to stop their medication and report to a physician immediately if jaundice or abnormally dark or brown urine is noted.

Primaquine use is contraindicated in pregnancy. *P. vivax* or *P. ovale* infections occurring during pregnancy should be treated with standard doses of chloroquine (Table 8). Relapses can be prevented by weekly chemoprophylaxis with choloroquine until after delivery, when primaquine can be safely used for mothers with normal G6PD levels.

QUININE AND QUINIDINE

Mechanism of Action: These quinoline-containing antimalarials are alkaloid derivatives of cinchona bark that act on the intraerythrocytic asexual stage of the parasite.

Indications and Efficacy: Quinine and quinidine are indicated only for the treatment of malaria. Quinine (or quinidine) should not be used alone: a second drug such as doxycycline should be used concurrently (see Section 8).

Oral therapy with quinine (with a second agent) is indicated for the treatment of non-complicated falciparum malaria and as step-down therapy (with a second agent) after parenteral treatment of complicated malaria. Oral quinidine is often used for these purposes in children, because quinidine is easier to suspend into liquid formulation.

Quinine is the preferred drug for parenteral therapy of severe or complicated malaria (see Table 5, WHO criteria) because of the significant cardiotoxic effects associated with parenteral quinidine and the requirement for cardiac monitoring.

Adverse Effects, Contraindications and Precautions: Minor adverse events are common with quinine and quinidine use. These include cinchonism (tinnitus, nausea, headache, blurred vision), hypoglycemia, nausea, and vomiting. Occasionally, hypersensitivity and nerve deafness have been reported. Parenteral quinidine has the potential to increase the QTc and therefore requires electrocardiographic monitoring.

OTHER DRUGS NOT AVAILABLE OR NOT ROUTINELY RECOMMENDED IN CANADA (IN ALPHABETICAL ORDER)

It is important for travellers and providers to understand that the medical management of malaria in countries where the disease is endemic may differ significantly from management in Canada. In countries where malaria is endemic there may be a limited number of effective medications available for treatment, indeed some of the drugs used may be ineffective in non-immune travellers or be associated with unacceptable adverse outcomes. As well, the level of health care available in some of these countries may put travellers at risk of other infectious diseases.

AMODIAQUINE is a 4-aminoquinoline that was first introduced as an alternative to chloroquine. Unfortunately, resistance to this drug has followed the path of chloroquine resistance.

ARTEMISININ AND DERIVATIVES are endoperoxide-containing natural antimalarials from sweet wormwood (*Artemisia annua*). They are being used for the treatment of malaria in many parts of the world. Artemesinin (qinghaosu) derivatives – including artesunate, artemether, arteether, and dihydroartesinin – are available in oral, parenteral, and suppository formulations. They are all metabolized to a biologically active metabolite, dihydroartemesinin, and have their antiparasitic effects on the younger, ring-forming parasites. They thereby decrease the numbers of late parasite forms that can obstruct the host's microvasculature.

All artemisinin preparations have been studied and used for treatment only. They are **not** recommended for prophylaxis because of their short half-life. For the treatment of severe and complicated malaria, all compounds are at least as efficacious as quinine. Qinghaosu and its derivatives lead to faster clearance times of parasites (mean: 32% faster) and fever (mean: 17% faster) than do any other antimalarials. In spite of the more rapid antiparasitic action of qinghaosu compounds, these agents have not been shown to decrease mortality as compared with quinine.

Artemisinin-related compounds act rapidly against drug-resistant *P. falciparum* strains but have high recrudescence rates (about 10% to 50%) when used as monotherapy for < 5 days. Recent studies have examined longer durations of therapy (7 days), and combinations of qinghaosu derivatives and mefloquine to prevent recrudescence. *In vitro* synergy has been demonstrated between artemisinin derivatives, mefloquine, and tetracycline. In Thailand, treatment with oral artesunate (over 3 to 5 days) combined with mefloquine (15 to 25 mg/kg) was more effective than mefloquine or artesunate alone. Combination therapy results in > 90% cure rates of primary and recrudescent *P. falciparum* infections.

Artemisinin derivatives have been used in over 1 million patients and are well tolerated. To date, there

have been two human cases of complete heart block associated with their use, but most volunteer and clinical studies have found no evidence of cardiac or other toxic effects. Neurological lesions involving the brainstem have been seen in rats, dogs, and primates given repeated doses of artemisinin derivatives. To date, no clinical neurologic events have been observed in humans; however, studies addressing cumulative toxic effects in humans have not been performed. The safety of qinghaosu derivatives in pregnancy has not been established.

Artemisinin and its derivatives are now available and increasingly used in Southeast Asia and Africa; none is licensed in Canada. Coartemether (Riamet in Europe, Coartem in Africa) is a combination of artemether and lumefantrine that is currently licensed in some European countries and is becoming widely distributed in Africa for the treatment of malaria. Combinations of artesunate and mefloquine appear to be the most active drug regimens for treatment of multidrug-resistant falciparum malaria in Southeast Asia. There is concern that the quality of artemisinin derivatives available in developing countries may be questionable, as they may not be produced in accordance with the good manufacturing production standards required in North America.

Although there is good evidence that therapy with artemisinin compounds is safe, questions about cumulative neurologic toxicity require resolution.

Recommendations

i. Artemisinin compounds are effective alternative therapies for multidrug-resistant malaria (complicated and uncomplicated) (AI – evidence-based medicine recommendation). However, at present, there are insufficient toxicity data and evidence of clinical superiority over standard therapy to routinely recommend these as first-line agents, particularly for *P. falciparum* infections acquired in Africa.

ii. Artemisinin compounds should **not** be used for chemoprophylaxis (C III – evidence-based medicine recommendation).

iii. Artemisinin compounds may be considered for the treatment of laboratory-confirmed severe falciparum malaria acquired in areas where *P. falciparum* is known to be multidrug-resistant OR for the treatment of falciparum malaria that fails standard drug regimens. In such cases, they should be used in combination with mefloquine or tetracycline/doxycycline (A I – evidence-based medicine recommendation).

HALOFANTRINE is a phenanthrene methanol derivative related to mefloquine and quinine. It is available only in an oral formulation, which is limited by variable bio-availability. Halofantrine is not licensed in Canada and has recently been withdrawn from the world market because of concerns about cardiotoxicity. It does remain widely available in the tropics, and travellers should be made aware of the danger of this drug. The WHO has reported cardiac deaths associated with the use of halofantrine and no longer recommends its use.

Recommendations

i. Halofantrine should **not** be used for self-directed therapy (D II – evidence-based medicine recommendation).

ii. Halofantrine is **not** indicated for the treatment of multidrug-resistant malaria (combined resistance to mefloquine and chloroquine) or for the treatment of recrudescent malaria (D II – evidence-based medicine recommendation).

iii. Travellers who inquire about halofantrine or who are likely to encounter its use (e.g., in West Africa) should be informed of its potential cardiotoxic effects (C III – evidence-based medicine recommendation).

PROGUANIL should **not** be used as a single agent for chemoprophylaxis. Proguanil is well tolerated. Although oral aphthous ulcerations are not uncommon, they are rarely severe enough to warrant discontinuing this medication. Proguanil is considered safe during pregnancy and breast-feeding, but insuffi-

cient drug is excreted in the milk to protect a nursing infant.

PYRIMETHAMINE-SULFADOXINE (Fansidar®) is a fixed drug combination antimetabolite that inhibits parasite folate synthesis. Historically, this drug has been used for treatment, including self-treatment, of *P. falciparum*, but increasing resistance means that it has limited utility for the treatment of *P. falciparum* and is no longer recommended. Resistance has been reported in the Amazon Basin, Southeast Asia, and increasingly throughout Africa.

Pyrimethamine-sulfadoxine is not recommended by CATMAT, the Centers for Disease Prevention and Control, or WHO for chemoprophylaxis because of the life-threatening complication of Stevens-Johnson syndrome and toxic epidermal necrolysis.

PYRONARIDINE is a benzonaphthyridine synthesized in China in 1970, which has been used for the treatment of *P. vivax* and *P. falciparum* for more than 20 years and has been shown to be effective in the treatment of falciparum malaria in children in Cameroon. It has more gastrointestinal side effects than chloroquine. There are insufficient data at present to recommend the use of pyronaridine for the treatment of malaria in non-immune travellers.

TAFENOQUINE is a long-acting, 8-aminoquinoline with a half-life measured in weeks rather than hours. Initial research has shown efficacy with weekly chemoprophylaxis and evidence of causal prophylaxis. Studies are ongoing in semi- and non-immune individuals. In the future, tafenoquine may provide another option for chemoprophylaxis in those without G6PD deficiency.

Table 8. Drugs for the treatment and prevention of malaria

Drug, generic (trade) name	Indication	Adult dosage	Pediatric dosage	Advantage	Disadvantage	Adverse effects
ATOVAQUONE / PROGUANIL (ATQ/PG) (Malarone®)	Prevention and treatment of *P. falciparum*	**Adult tablet:** 250 mg atovaquone plus 100 mg proguanil **Prevention:** 1 tablet daily **Treatment:** 1000 mg atovaquone AND 400 mg proguanil (4 tablets) once daily x 3 days	**Adult tablets** Prevention: 11-20 kg: ¼ tablet daily 21-30 kg: ½ tablet daily 31-40 kg: ¾ tablet daily > 40 kg: 1 tablet daily **Treatment:** 20 mg/kg atovaquone AND 8 mg/kg proguanil once daily x 3 days 11-20 kg: 1 tablet daily 21-30 kg: 2 tablets daily 31-40 kg: 3 tablets daily ≥ 41 kg: 4 tablets daily	Causal prophylaxis – only have to continue for 7 days after exposure	Daily dosing for prophylaxis	**Frequent:** Nausea, vomiting, abdominal pain, diarrhea, increased transaminases **Rare:** Seizures, rash, mouth ulcers
CHLOROQUINE (Aralen®) Tablet: 150 mg base	Prevention and treatment in chloroquine-sensitive *P. falciparum* areas Treatment of *P. vivax, P. ovale, P. malariae*	**Prevention:** 300 mg base once weekly **Treatment:** 1.5 g base over 3 days	**Prevention:** 5 mg/kg base weekly; maximum 300 mg **Treatment:** 25 mg base/kg total over 3 days	Long-term safety data for prophylaxis	Most areas now report chloroquine resistance	**Frequent:** Pruritis in black-skinned individuals, nausea, headache **Occasional:** Skin eruptions, reversible corneal opacity **Rare:** Nail and mucous membrane discoloration, partial alopecia, photophobia, nerve deafness, myopathy, retinopathy with daily use, blood dyscrasias, psychosis and seizures

Table 8. Drugs for the treatment and prevention of malaria (continued)

Drug, generic (trade) name	Indication	Adult dosage	Pediatric dosage	Advantage	Disadvantage	Adverse effects
CLINDAMYCIN (Dalacin C®)	Alternative treatment for *P. falciparum* with a second drug if standard therapy contraindicated	**Prevention:** no indication **Treatment oral:** 300 mg base every 6 hr for 5 days **Treatment IV:** 10 mg/kg (loading dose) intravenously, followed by 5 mg/kg every 8 hours until blood is cleared of asexual parasites or oral therapy is tolerated. NOTE: Should only use if patient is unable to take doxycycline or ATQ/PG	**Prevention:** no indication **Treatment oral:** 5 mg/kg three times per day for 5 days **Treatment IV:** 10 mg/kg (loading dose) intravenously, followed by 5 mg/kg every 8 hours until blood is cleared of asexual parasites or oral therapy is tolerated. NOTE: Should only use if patient is unable to take doxycycline or ATVPG	Safe in pregnancy and young children	Lower efficacy than atovaquone/proguanil alone or combination of doxycycline plus quinine	**Frequent:** Diarrhea, rash **Occasional:** Pseudomembranous colitis **Rare:** Hepatotoxicity, blood dyscrasias
DOXYCYCLINE (Vibra-Tabs™)	Prevention and treatment of chloroquine-resistant *P. falciparum*	**Prevention:** 100 mg once daily **Treatment:** 100 mg twice daily for 7 days	**Prevention:** 1.5 mg base/kg once daily (max 100 mg) < 25 kg or < 8 yr: contraindicated 25-35 kg or 8-10 yr: 50 mg 36-50 kg or 11-13 yr: 75 mg ≥ 50 kg or ≥ 14 yr: 100 mg **Treatment:** 1.5 mg base/kg twice daily (max. 200 mg daily) < 25 kg or < 8 yr: contraindicated 25-35 kg or 8-10 yr: 50 mg twice daily 36-50 kg or 11-13 yr: 75 mg twice daily ≥ 51 kg or ≥ 14 yr: 100 mg twice daily	Protection against leptospirosis	Daily dosing required for chemoprophylaxis	**Frequent:** Gastrointestinal upset, vaginal candidiasis, photosensitivity **Occasional:** Azotemia in renal diseases **Rare:** Allergic reactions, blood dyscrasias, esophageal ulceration

Table 8. Drugs for the treatment and prevention of malaria (continued)

Drug, generic (trade) name	Indication	Adult dosage	Pediatric dosage	Advantage	Disadvantage	Adverse effects
MEFLOQUINE (Lariam®)	Prevention of *P. falciparum*	**Prevention:** 250 mg base once weekly **Treatment:** not routinely recommended, see text	**Prevention:** 5 mg/kg weekly < 5 kg: no data 5-9 kg: ⅛ tablet 10-19 kg: ¼ tablet 20-29 kg: ½ tablet 30-45 kg: ¾ tablet ≥ 46 kg: 1 tablet **Treatment:** not routinely recommended, see text	Weekly dosing Long-term safety data	There have been occasional publicized cases of severe intolerance to mefloquine, which may result in increased concern. If mefloquine is the best choice but concern is expressed, consider either a loading dose or start 3 weeks before departure to test for tolerability.	**Frequent:** Dizziness, headache, sleep disorders, nightmares, nausea, vomiting, diarrhea **Occasional:** Sensory and motor neuropathies, seizures, abnormal coordination, confusion, hallucinations, forgetfulness, emotional problems including anxiety, aggression, agitation, depression, mood changes, panic attacks, psychotic or paranoid reactions, restlessness **Rare:** Suicidal ideation and suicide (relation to drug administration not established)
PRIMAQUINE	Prevention of chloroquine-resistant *P. falciparum* Terminal prophylaxis *P. vivax* and *P. ovale* Radical cure for *P. vivax* and *P. ovale* infections	**Prevention:** **Primary prophylaxis** 30 mg base daily, see text **Terminal prophylaxis or radical cure:** 30 mg base/day for 14 days	**Prevention:** **Primary prophylaxis** 0.5 mg base/kg daily, see text **Terminal prophylaxis or radical cure:** 0.5 mg base/kg daily for 14 days	Causal prophylaxis – only have to continue for 7 days after exposure	Daily dosing Require G6PD* testing, see text	**Occasional:** GI upset, hemolysis in G6PD deficiency, methemoglobinemia

Table 8. Drugs for the treatment and prevention of malaria (continued)

Drug, generic (trade) name	Indication	Adult dosage	Pediatric dosage	Advantage	Disadvantage	Adverse effects
QUINIDINE GLUCONATE/ SULFATE		**Prevention:** no indication **Treatment:** see Table 7	**Prevention:** no indication **Treatment:** see Table 7. 28 mg base/kg daily, divided q 8 hourly.**		Parenteral therapy requires cardiac monitoring	**Frequent:** Vomiting, cramps, cinchonism (tinnitus, nausea, headache, blurred vision) **Occasional:** Widening of QRS complex, cardiac disturbance, fever, delirium, rashes **Rare:** Acute hemolytic anemia
QUININE DIHYDRO-CHLORIDE		**Prevention:** no indication **Treatment:** See Table 7	**Prevention:** no indication **Treatment:** See Table 7			**Frequent:** Cinchonism (tinnitus, nausea, headache, blurred vision), hypoglycemia **Occasional:** Cardiac conduction disturbances, hypersensitivity **Rare:** Hemolysis
QUININE SULPHATE (Novoquinine®)		**Prevention:** no indication **Treatment oral:** 500 mg base three times daily for 3-7 days (7 days for S.E. Asia) **IV:** see Table 7	**Prevention:** no indication **Treatment oral:** 7.5 mg base/kg (max 500 mg base) three times daily for 3-7 days (7 days for S.E. Asia) **IV:** see Table 7			Similar to above

*Glucose-6-phosphate dehydrogenase

**Suggested mixing instructions: to make 120 mL solution of concentration 8.3 mg base/mL combine 60 mL Orasweet and 60 mL Oraplus with 6 x 200 mg tablets of crushed quinidine sulfate.

APPENDIX I

Malaria Risk by Geographic Area in Countries with Endemic Malaria†

Country	Areas of risk within country	Recommended regimens
Afghanistan	All areas below 2000 m	**First-line agent***
Algeria	One small focus in Ihrir	Chloroquine in risk area
Angola	All	**First-line agent***
Argentina	Rural areas near Bolivian and Paraguay borders, lowlands of Salta and JuJuy provinces, and lowlands of Misiones and Corrientes Provinces	Chloroquine
Armenia	Risk limited to western border areas: Masis, Ararat, and Artashat regions in Ararat district. No risk in tourist areas.	Chloroquine
Azerbaijan	Rural lowlands with highest risk in areas between Kura and Arax rivers	Chloroquine
Bangladesh	All, except no risk in city of Dhaka	**First-line agent***
Belize	Rural areas including resort areas, off shore islands, and forest preserves, except no risk in Belize City	Chloroquine
Benin	All	**First-line agent***
Bhutan	Risk in southern belt of five districts: Chirang, Samchi, Samdrupjongkhar, Sarpang, and Shemgang	**First-line agent***
Bolivia	Rural areas < 2500 metres, risk in departments of Beni, Cochabamba, Chuquisaca, La Paz, Pando, Santa Cruz, and Tarija	**First-line agent***
Botswana	Northern part of country (north of 21° South)	**First-line agent***
Brazil	Risk in Acre and Rondonia states, territories of Amapa and Roraima, and in rural areas of Amazonas, Maranhao, Mato Grosso, Para (except Belem City), and Tocantins. There is also transmission in urban areas, including large cities such as Porto Velho, Boa Vista, Macapa, Manaus, Santarem, and Maraba **Note:** No risk for travellers to coastal states from the horn to Uruguay border and Iguassu Falls.	**First-line agent***
Burkina Faso	All	**First-line agent***
Burma: see Myanmar		
Burundi	All	**First-line agent***
Cambodia	All, except no risk in Phnom Penh. Malaria risk exists in Angkor Wat.	**First-line agent*** (on western borders - doxycycline or atovaquone/ proguanil)
Cameroon	All	**First-line agent***
Cape Verde	Limited risk exists on Sao Tiago Island.	**First-line agent***
Central African Republic	All	**First-line agent***
Chad	All	**First-line agent***

Country	Areas of risk within country	Recommended regimens
China	Rural areas only in Anhui, Fujian, Guangdong, Guangxi, Guizhou, Hainan, Hubei, Hunan, Jiangsu, Jiangxi, Shandong, Shanghai, Sichuan, Xizang, Yunnan and Zhejiang provinces/autonomous regions. In provinces with risk, transmission only occurs during warm weather. Transmission occurs < 1500 metres from July to November north of 33° North, from May to December between 33° North and 25° N and throughout the year below 25° North. **Note:** Travellers visiting cities and popular rural tourist routes, including Yangtze river cruises, are generally not at risk and require no prophylaxis.	Chloroquine **First-line agent*** for Hainin province,Yunnan province and Guangxi province
Colombia	In general, rural areas only below 800 m, no risk in Bogota and vicinity	**First-line agent***
Comoros	All	**First-line agent***
Congo	All	**First-line agent***
Costa Rica	Risk in the provinces of Alajuela, Limon, Guanacaste, and Heredia. No risk in Limon City.	Chloroquine
Côte d'Ivoire (formerly Ivory Coast)	All	**First-line agent***
Democratic Republic of Congo	All	**First-line agent***
Djibouti	All	**First-line agent***
Dominican Republic	All rural areas. Highest risk in areas bordering Haiti. Travellers visiting resort areas are generally not at risk and require no prophylaxis.	Chloroquine
East Timor	All	**First-line agent***
Ecuador	All areas less than 1500 metres (no risk in Guayaquil, Quito and vicinity, the central highland tourist areas or the Galapagos Islands)	**First-line agent***
Egypt	Limited risk in El Faiyum area and part of Southern (upper) Egypt (no risk in main tourist areas including Nile cruises)	None
El Salvador	Rural areas of the departments of Santa Ana, Ahuachapan, and La Union.	Chloroquine
Equatorial Guinea	All	**First-line agent***
Eritrea	All, except no risk in Asmara and above 2000 metres	**First-line agent***
Ethiopia	All, except no risk in Addis Ababa and above 2000 metres	**First-line agent***
French Guiana	All	**First-line agent***
Gabon	All	**First-line agent***
Gambia	All	**First-line agent***
Georgia	Risk in the southeastern part of the country, in the districts of Lagodekhi, Sighnaghi, Dedophilistskaro, saraejo, Gardabani and Marneuli in the Kakheti and Kveno Kartli regions. No risk in Tbilisi.	Chloroquine
Ghana	All	**First-line agent***
Guatemala	Rural areas only, except no risk in central highlands above 1500 metres. No risk in Antigua or Lake Atitlan.	Chloroquine
Guinea	All	**First-line agent***

Country	Areas of risk within country	Recommended regimens
Guinea-Bissau	All	**First-line agent***
Guyana	High risk in all of interior regions. Sporadic cases reported in the coastal region.	**First-line agent***
Haiti	All	Chloroquine
Honduras	Rural areas only, including Roatan and other Bay Islands	Chloroquine
Hong Kong S.A.R. (China)	Urban areas: no risk, limited risk in extremely rural areas of S.A.R.	None
India	All areas below 2000 metres including Delhi and Bombay, except no transmission in parts of the states of Himachal Pradesh, Jammu, Kashmir, and Sikkim	**First-line agent***
Indonesia	In general, rural areas only, except high risk in all areas of Irian Jaya (western half of island of New Guinea). No risk in cities of Java and Sumatra or resort areas in Java or Bali. **Note:** Transmission is largely confined to rural areas not visited by most tourists. Risk exists at the temple complex of Borobudur on Java.	**First-line agent***
Iran, Islamic Republic of	Rural areas only in the provinces of Sistan-Baluchestan, the southern part of Kerman and Hormozgan	**First-line agent***
Iraq	All areas in northern region: Duhok, Erbil, Basrah, Tamim, Ninawa and Sulaimaniya province	Chloroquine
Ivory Coast: see Côte d'Ivoire		
Kenya	All areas **including game parks** except low risk in city of Nairobi and above 2500 metres	**First-line agent***
Korea, Democratic People's Republic of (North)	Limited malaria risk in some southern areas. No risk in Pyongyang.	Chloroquine
Korea, Republic of (South)	Risk limited to demilitarized zone and to rural areas in the northern parts of Kyonggi and Kangwon provinces along the demilitarized zone	Chloroquine
Lao People's Democratic Republic	All areas, except no risk in city of Vientiane	**First-line agent***
Liberia	All	**First-line agent***
Madagascar	All	**First-line agent***
Malawi	All	**First-line agent***
Malaysia	Risk limited to rural areas only. No risk in urban or coastal areas, no risk in Republic of Singapore.	**First-line agent***
Mali	All	**First-line agent***
Mauritania	All areas, except no risk in the northern areas of Dakhlet-Nouadhibou and Tiris-Zemour	**First-line agent***
Mauritius	Rural areas only, except no risk in Rodrigues Island	Chloroquine
Mayotte	All	**First-line agent***
Mexico	Rural areas including rural resort areas of the following states: Campeche, Chiapas, Chihauhua, Durango, Guerrero, Hidalgo, Jalisico (mountainous northern area only), Michoacan, Nayarit, Oaxaca, Quintana Roo, Sinaloa, Sonora and Veracrus. Risk also exists in area between 24°N and 28°N latitiude and 106°W and 110°W longitude. No risk along U.S. border. No malaria risk along the Pacific and Gulf coasts.	Chloroquine

Country	Areas of risk within country	Recommended regimens
Morocco	Very limited risk in rural areas of Khouribga province. The cities of Tangier, Rabat, Casablanca, Marrakech and Fes have no risk.	None
Mozambique	All	**First-line agent***
Myanmar (formerly Burma)	Rural areas. **Note:** Travellers to Yangon (Rangoon) and Mandalay are not at risk and need no prophylaxis.	**First-line agent*** Doxycyline or atovaquone/ proguanil for borders with Thailand
Namibia	Risk in the northern regions and in Omaheke and Otjozondjupa and along the Kavango and Kunene rivers	**First-line agent***
Nepal	Rural areas in Terai District and hill districts below 1200 metres. No risk in Kathmandu and typical Himalayan treks.	**First-line agent***
New Hebrides: see Vanuatu		
Nicaragua	Rural areas only, however risk occurs in the outskirts of Managua.	Chloroquine
Niger	All	**First-line agent***
Nigeria	All	**First-line agent***
Oman	Limited risk in remote areas of Musandam Province	**First-line agent***
Pakistan	All areas below 2000 metres including cities	**First-line agent***
Panama	Risk in rural areas of 3 provinces: Bocas del Toro, Darien and San Blas. No risk in the Canal Zone or in Panama City.	Chloroquine in Bocas del Toro **First-line agent*** in Darien, San Blas and San Blas Islands
Papua New Guinea	All	**First-line agent***
Paraguay	Risk in 3 departments: Alto Parana, Caaguazu, and Canendiyu	Chloroquine
Peru	Risk in all departments except Arequipa, Moquegua, Puno and Tacna. Note: no risk for travellers visiting only Lima and vicinity, coastal areas south of Lima, or the highland tourist areas (Cuzco, Machu Picchu, Lake Titicaca).	**First-line agent***
Philippines	Rural areas only, except no risk in Manila and province of Bohol, Catanduanes and Cebu	**First-line agent***
Rwanda	All	**First-line agent***
Sao Tome and Principe	All	**First-line agent***
Saudi Arabia	All areas in Western province, except no risk in the high altitude areas of Asir province (Yemen border), and the urban areas of Jeddah, Mecca, Medina and Taif	**First-line agent***
Senegal	All	**First-line agent***
Sierra Leone	All	**First-line agent***
Solomon Islands	All	**First-line agent***
Somalia	All	**First-line agent***
South Africa	Risk in the low altitude areas of the Mpumalanga Province (including Kruger National Park), Northern Province and northeastern KwaZulu-Natal as far south as Tugelan River	**First-line agent***
Sri Lanka	All rural areas except no risk in district of Colombo, Kalutara, and Nuwara Eliya.	**First-line agent***
Sudan	All	**First-line agent***
Suriname	Rural areas only, except no risk in Paramaribo district and coastal areas north of 5° North	**First-line agent***

Country	Areas of risk within country	Recommended regimens
Swaziland	All lowland areas	**First-line agent***
Syrian Arab Republic	Rural areas only (May to October) especially along northern border. No risk in districts of Damascus, Deir-es-zor and Sweida.	Chloroquine
Tajikistan	Risk predominantly in southern border areas (Khatlon region); risk in some central (Dushanbe), western (Gorno-Badakhshan) and northern (Leninabad) areas.	Chloroquine
Tanzania, United Republic of	All	**First-line agent***
Thailand	Malaria risk exists throughout the year in rural, especially forested and hilly, areas of the whole country, mainly towards the international borders (not visited by most travellers). There is no risk in cities and the main tourist resorts (e.g., Bangkok, Chiangmai, Chiang Rai, Pattaya, Phuket, and Ko Samui). Mefloquine resistance reported from areas on borders with Myanmar and Cambodia.	Doxycycline or atovaquone/proguanil for overnight exposure in rural areas on border with Myanmar and Cambodia.
Togo	All	**First-line agent***
Turkey	Cukurova/Amikova areas and southeast Anatolia (May to October). No risk in main tourist areas in west and south-west or the Incirlik U.S. Air Force base.	Chloroquine
Turkmenistan	Risk in some villages from June to October in the Mary district	Chloroquine
Uganda	All	**First-line agent***
Vanuatu (formerly New Hebrides)	All	**First-line agent***
Venezuela	Risk in the rural areas of the following states: Apure, Amazonas, Barinas, Bolivar, Sucre, Tachira, and Delta Amacuro. Risk in Angel Falls.	**First-line agent***
Viet Nam	Rural areas only. No risk in Red Delta and coastal plain north of Nha Trang	**First-line agent***
Yemen	All except no risk at elevations above 2000 metres. No risk in Sanas (2230 metres)	**First-line agent***
Zaire: see Democratic Republic of Congo		
Zambia	All	**First-line agent***
Zimbabwe	All (including Victoria Falls) except no risk in cities of Harare and Bulawayo	**First-line agent***

Countries not listed are considered free of malaria.

†Adapted from *CDC Health Information for International Travel 2001* and WHO *International Travel and Health 2003*.

***First-line agent** (for chloroquine-resistant area) = atovoquone/proguanil; doxycycline or mefloquine (alphabetical listing).

APPENDIX II

Strength and Quality of Evidence Summary*

Category	Definition
Categories for the strength of each recommendation	
A	Good evidence to support a recommendation for use.
B	Moderate evidence to support a recommendation for use.
C	Poor evidence to support a recommendation for or against use.
D	Moderate evidence to support a recommendation against use.
E	Good evidence to support a recommendation against use.
Categories for the quality of evidence on which recommendations are made	
I	Evidence from at least one properly randomized, controlled trial.
II	Evidence from at least one well-designed clinical trial without randomization, from cohort or case-controlled analytic studies, preferably from more than one centre, from multiple time series, or from dramatic results in uncontrolled experiments.
III	Evidence from opinions or respected authorities on the basis of clinical experience, descriptive studies, or reports of expert committees.

*From Macpherson DW. *Evidence-based medicine.* CCDR 1994; 20:145-47.

APPENDIX III

Instructions for Insecticide Treatment of Bed Nets and Clothing

How to Treat Mosquito Nets with Insecticides (adapted from PATH Canada)

Before travelling, individuals should inquire about the availability of insecticides and should plan to purchase and apply these products at their destination. Pre-impregnated mosquito nets are available from PATH Canada (www.pathcanada.org) and are found in some travel and mountain equipment stores in Canada and the United States. These products are not currently registered by the Pest Management Regulatory Agency (PMRA). For information regarding the availability of insecticides in subSaharan Africa for application onto clothing or nets, see the PATH Canada Website.

Always use metric measurements: centimetre (cm), metre (m), millimetre (mm) millilitre (mL) and litre (L). All nets should be clean and dry. **Always** wear protective gloves when soaking a net in insecticide.

1. Calculate the area of the net, in square metres.

   Consider a conical net as a triangle and a rectangular net as two rectangles.

   How to measure a mosquito net:

   Conical net

   Lay the net flat:

   - Measure the total distance around the curved base of the net (m)
   - Measure the height (m)
   - Multiply base x height = area of net

   Rectangular net

   Hang the net up:

   - Measure the area of the top = width x length
   - Measure the area around the sides = height x total distance around base of net
   - Add the two measurements together to find the total area of the net

2. Calculate the amount of water absorbed by the net, in millilitres or litres.

   Using a bucket and a measuring container, measure 2 L of water into the bucket. Soak the net until it is totally wet. Carefully wring out the net over the bucket. When the net has stopped dripping, measure the water remaining in the bucket.

   For example:

   - Original water in bucket (2 L) minus remaining water in bucket (1.3 L) = water absorbed by the net (0.7 L or 700 mL)

3. Calculate the amount of insecticide required

   - Obtain the highest quality product, in original packaging, specifically designed for use on mosquito netting. Avoid use of products that have not undergone meticulous quality control. Do not use substitute products.
   - Check the recommended dose of insecticide. Read the instructions on the bottle or check the following Table.

- Check the concentration of the insecticide. This follows the name of the insecticide. For example, permethrin EC 50 contains 500 g of insecticide in each litre; this is also known as a 50% solution.

Doses of commonly used insecticides (in mg of insecticide per square metre of material – polyester)	
Compound and formulation	**Dose (mg of active ingredient/square metre)**
Permethrin EC	200-500
Deltamethrin SC	15-25
Deltamethrin tablet	1 tablet per net
Lambda-cyhalothrin CS	10-15
Cyfluthrin EW	30-50
Alpha-cypermethrin SC	20

To calculate the amount of insecticide use the following formula:

- Dose (mg/unit metre) x area of net (in square metres) to determine the amount of insecticide required in mg (remember there are 1000 mg per gram, 1000 mL per litre, and 1 gram per mL).
- Take amount of insecticide required **divided by** the amount in mg of insecticide per mL of product (for example, a product that contains 50% permethrin will contain 500 g permethrin/litre and therefore 500 mg permethrin/mL) = amount of insecticide required in mL.

For example:

If you want a dose of 200 mg/square metre on an 11 square metre net and you are using a product containing 50% permethrin w/w, you would calculate the amount required as follows:

- 200 mg/square metre x 11 metres squared = 2200 mg permethrin required.
- 50% permethrin = 500 mg permethrin/mL.
- 2200 mg **divided by** 500 mg/mL = 4.4 mL of insecticide required to treat the net.

If you have found that your net absorbs 0.7 litre (700 mL) of water, add this amount of water to the insecticide to make a final mixture.

4. Wear protective gloves when treating nets with insecticide.
5. Measure the amount of water and insecticide needed.

   Wide-mouth containers, such as an empty margarine container (1 kg = approximately 1 litre), are best for measuring large amounts of water. Insecticide can be measured using a 250 mL empty container, which can be scored inside at 50 mL intervals. For small amounts of insecticide a syringe could be used.
6. Add the insecticide to the water and mix well.

   Treatment should be performed out of doors or in a well-ventilated area. Alternatively, you can place the net in a plastic bag (making sure there are no holes in the bag), add the insecticide and water solution, knead well, and remove the treated net from the bag for drying.
7. Dip the net into the solution until it is thoroughly wet.
8. Wring the net out over a bowl and hang it up until it has stopped dripping.
9. Dry the net.

   Wet nets can be laid out flat to dry. Do not place them in direct sunlight for more than a few hours, as UV exposure may reduce the efficacy of the insecticide.
10. Wash your hands and all equipment with soap and water. Triple rinse any containers that will be reused, and punch holes in containers or equipment that will be discarded to prevent their reuse as drinking water containers.
11. Pour any waste insecticide down a pit latrine or into a pit dug into the ground and NOT into a river or pond, as pyrethroids are highly toxic to fish and aquatic invertebrates.

For more information regarding application of insecticides onto mosquito netting, see PATH Canada Website at <www.pathcanada.org>.

How to Treat Clothing with Insecticides
(adapted from Sawyer Products)

Before travelling, individuals should inquire about the availability of insecticide and should plan to purchase and apply these products at their destination. These products are not currently registered by the PMRA.

1. Select an area that is well ventilated, but out of the wind. Do not spray in an enclosed area.
2. Lay clothing flat on the ground, pin clothes on a clothesline, drape over porch furniture and railings, or hang clothes on separate clothes hangers, so that each garment can be easily sprayed and allowed to thoroughly dry.
3. One treatment with permethrin spray will remain effective for 2 weeks, including weekly launderings. An amount of 100 mL (3 fluid ounces) of permethrin spray will treat one complete set of garments (a pair of long-legged trousers and a long-sleeved shirt). Jackets, windbreakers, and rain gear may be treated in the same manner (caution: permethrin does not adhere well to some synthetic fibres).
4. Wear protective gloves.
5. Spray one side of the garment for approximately 60 seconds holding the spray can or bottle upright and 15-20 cm away from the surface. Spray in a slow sweeping motion, similar to spraying paint, to evenly coat the entire surface. Turn the garment around to the other side and repeat by spraying the second side for 60 seconds. The surface of the clothing should be wetted but not completely saturated with spray.
6. Hang garments up and allow the permethrin treatment to dry for 2 hours, or 4 hours if conditions are very humid.
7. Treating other garments and gear (**do not treat underwear**):
    - Socks can be treated with permethrin spray. Lay socks on the ground or pin on a clothesline, and lightly spray the upper parts of socks. Allow to dry for 2 or more hours.
    - Polyurethane-coated nylon (synthetic) tent flaps and doors can be treated with permethrin spray. Erect tent outdoors and spray all tent flaps and doors until wetted. Leave standing for 2 or more hours to dry.
8. After garments have dried, pack them as you normally would for your trip. You may also want to roll up your treated clothes and store them in a plastic bag to keep them dry. Pack tents as you normally would.

For more information regarding application of insecticides onto clothing, see <www.permethrin-repellent.com>.

APPENDIX IV

Checklist for Travellers to Malarial Areas

The following is a checklist of key issues to be considered in advising travellers. The numbers in parentheses refer to those pages in the text where these issues are discussed in detail.

a) Risk of malaria (Appendix I)

Travellers should be informed about their individual risk of malaria infection and the presence of drug-resistant *P. falciparum* malaria in their areas of destination. Those who are pregnant, travelling with young children, or who have medical conditions that put them at increased risk (see Section 4) should question the necessity of the trip.

b) Anti-mosquito measures (page 3)

Travellers should be instructed on how to protect themselves against mosquito bites.

c) Chemoprophylaxis (page 10)

Travellers should be

1. questioned about medical conditions, drug allergies and other contraindications for drug use.
2. advised to start chemoprophylaxis before travel as directed, and to use prophylaxis continuously while in malaria-endemic areas and for 4 weeks after leaving such areas (except for atovaquone/proguanil and primaquine, which are taken for 1 week after leaving such areas).
3. informed that antimalarial drugs can cause side effects; if these side effects are serious, medical help should be sought promptly and use of the drug discontinued. Mild nausea, occasional vomiting or loose stools should not prompt discontinuation of chemoprophylaxis, but medical advice should be sought if symptoms persist.
4. warned that they may acquire malaria even if they use malaria chemoprophylaxis.
5. warned that they may receive conflicting information regarding antimalarial drugs overseas, but that they should continue their prescribed medication unless they are experiencing moderate to severe adverse effects.

d) In case of illness (Section 6)

Travellers should be informed that

1. symptoms of malaria may be mild, and that they should suspect malaria if they experience **a fever or 'flu like illness** (unexplained fever).
2. malaria may be fatal if treatment is delayed.
3. medical help should be sought promptly if malaria is suspected, and a blood film should be taken and examined for malaria parasites on one or more occasions (if possible, blood smears should be brought home for review).
4. self-treatment (if prescribed) should be taken only if prompt medical care is not available and medical advice should still be sought as soon as possible after self-treatment.
5. there is a need to continue to take chemoprophylaxis in cases of suspect or proven malaria.

e) Special hosts (Section 4)

1. Pregnant women, young children and those with underlying medical conditions require special attention because of the potential effects of malaria illness and the contraindication of certain drugs (for example, doxycycline in pregnant women and young children).

(Adapted from *International Travel and Health*, World Health Organization, Geneva, 1999).

APPENDIX V

Frequently Asked Questions About Malaria

From the Committee to Advise on Tropical Medicine and Travel, 2003

1. **Is malaria a serious infection for healthy people?**

   Malaria is a major killer worldwide and is the principal life-threatening infectious disease that Canadian travellers face when travelling to high-risk areas of the world. In recent years, there has been a dramatic increase in malaria cases among Canadian travellers, including several deaths.

2. **Do all travellers to the developing world need malaria prophylaxis?**

   Many destinations in the developing world are either free of malaria or the risk is so low that malaria prophylaxis is not needed. Furthermore, some travellers to countries with known malaria risk may not need to take malaria prophylaxis because malaria transmission is often confined to particular areas of a country (usually rural) and may be seasonal. For example, most individuals travelling only to urban centres or resort areas in Central and South America or Southeast Asia do not require malaria prophylaxis. However, **ALL** travellers (adults and children) to any area with any risk of malaria should use personal protective measures, such as treated mosquito nets and insect repellents, to avoid mosquito bites.

3. **Should pregnant women, babies and children receive malaria prophylaxis?**

   Pregnant women, babies and small children are at particular risk of serious malaria; if they must go to high-risk areas they should take malaria prophylaxis. Several effective prophylaxis regimens are known to be safe in these groups. It is important to remember that drugs taken by nursing mothers will not provide protection for the nursing child.

4. **Do most people who take malaria prophylaxis have serious side effects?**

   For travellers to high-risk areas, the risk of acquiring malaria and dying is significantly greater than the risk of experiencing a serious side effect from malaria prophylaxis. The great majority of people taking malaria prophylaxis (95% to 99%) have either no side effects or only mild and temporary ones, and in most studies only 1% to 4% of people have to change to an alternative drug because of side effects. These reactions are almost always reversible. Death from malaria, however, is not. The final choice of which antimalarial drug to use should be based on an individual risk assessment from a knowledgeable travel medicine provider, which should include issues such as the drug's effectiveness, the traveller's willingness to accept potential side effects, the convenience of dosing (weekly versus daily), the cost, and whether or not the traveller has any contraindications to the drug.

5. **Are there safer and/or more effective antimalarial drugs available?**

   For high-risk regions of the world with chloroquine-resistant malaria there are three drugs that are equally effective and currently licensed in Canada – atovaquone/proguanil (Malarone®), doxycycline (Vibra-tab®), and mefloquine (Lariam®). Each has advantages and disadvantages. Travellers should be cautious about drugs that are available and offered in other countries, since these drugs may be ineffective or more toxic, such as chloroquine, proguanil (Paludrine®), amodiaquine, pyrimethamine (Daraprim®), pyrimethamine plus sulfadoxine (Fansidar®), pyrimethamine plus

dapsone (Maloprim®). Before departure, travellers should consult a health care provider with knowledge of travel medicine for an informed recommendation regarding malaria prophylaxis for their planned itinerary.

6. **If I take prophylaxis, will the malaria I get be more resistant to treatment?**

   The prevention of malaria in travellers using prophylactic drugs does not promote the development of resistant malaria parasites. Appropriately used prophylaxis can actually reduce resistance by lowering the burden of malaria disease.

7. **Is there a limited period in which one can take prophylaxis safely?**

   There is no absolute time limit on how long one can take any antimalarial prophylactic drug. The small number of individuals who will experience significant side effects from antimalarial drugs usually do so within the first few weeks of use. If side effects are significant, then an alternative drug for malaria prevention should be used. Many mild side effects decrease with continued use of prophylaxis. If travellers consult a health care provider with knowledge of travel medicine early, then there may be time for a trial of the malaria prophylaxis before departure, to ensure tolerance.

8. **Is it true that some malaria cannot be treated?**

   If identified early and treated appropriately, almost all malaria can be completely cured. However, even short delays in the diagnosis of malaria can make treatment more difficult and less successful.

9. **Once you are infected with malaria, are you are infected for life?**

   Appropriate treatment and follow-up can ensure complete cure of malaria.

10. **Is it true that individuals born and raised in a malaria country are immune for life?**

    Over time, individuals raised in areas where malaria is common either die from the disease or become partially immune to its most serious manifestations. However, this immunity is short lived once an individual leaves a malarial area. Although avoidance of mosquito bites is important for protection (e.g., appropriate clothing, screens and mosquito nets, repellents), antimalarial prophylactic drugs are essential for optimal protection in most settings. Any individual who has travelled to malarial areas and subsequently develops fever should urgently seek medical advice (even if the fever appears many months after returning to Canada) and request blood films to rule out malaria.

Further information on issues related to travel medicine and contact information for travel medicine providers in your area is available through Health Canada's Travel Medicine Program at <www.travelhealth.gc.ca>.

APPENDIX VI

Contact Information for the Canadian Malaria Network

Parenteral quinine is the drug of choice for the treatment of severe and complicated malaria in Canada. To facilitate the acquisition of parenteral quinine, the Canadian Malaria Network (previously the Malaria Centres of Excellence) was established in conjunction with Health Canada's Travel Medicine Program to pre-position parenteral quinine stocks across Canada for the treatment of individuals with severe or complicated malaria. The main purpose of each of these centres is to provide, through the pharmacy, 24-hour access to this life-saving drug. As an additional service, if requested, the designated physician for each centre can provide assistance in management of malaria cases. These centres also gather surveillance data for all patients treated with parenteral quinine. The surveillance data (collected at time of diagnosis and on day 28) are essential in our efforts to improve malaria prevention, diagnosis, and management in Canada. The following hospital centres across Canada have been identified as participants in the Canadian Malaria Network. Each Centre will have depositories of parenteral quinine for the treatment of severe malaria and can provide guidance in the management of malaria infections.

To obtain parenteral quinine, please contact the listed pharmacy in your area. The designated physician for each Centre can be used as a resource for any questions you may have with regard to the treatment of malaria. For after-hours assistance please contact the infectious disease consultant on call at the appropriate Centre.

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